THE American Journal OF Gastroenterology

VOL. 26, NO. 2 AUGUST, 1956

Acute Gastritis as the Cause of Otherwise Unexplained Upper Gastrointestinal Hemorrhage

Massive Hematemesis Without Gross Lesion

The Behavior of Carcinoid Tumors of the Intestinal Tract

Evaluation of a New Atropine-Brand Anticholinergic

Third Annual Convention
New York, N. Y.
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1. Jacobson, P.: West. J. Surg. *63*:711 (Dec.) 1955. 2. Menger, H. C.: J.A.M.A. *159*:546 (Oct. 8) 1955.

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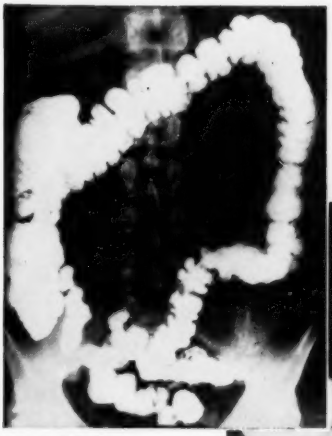

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THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

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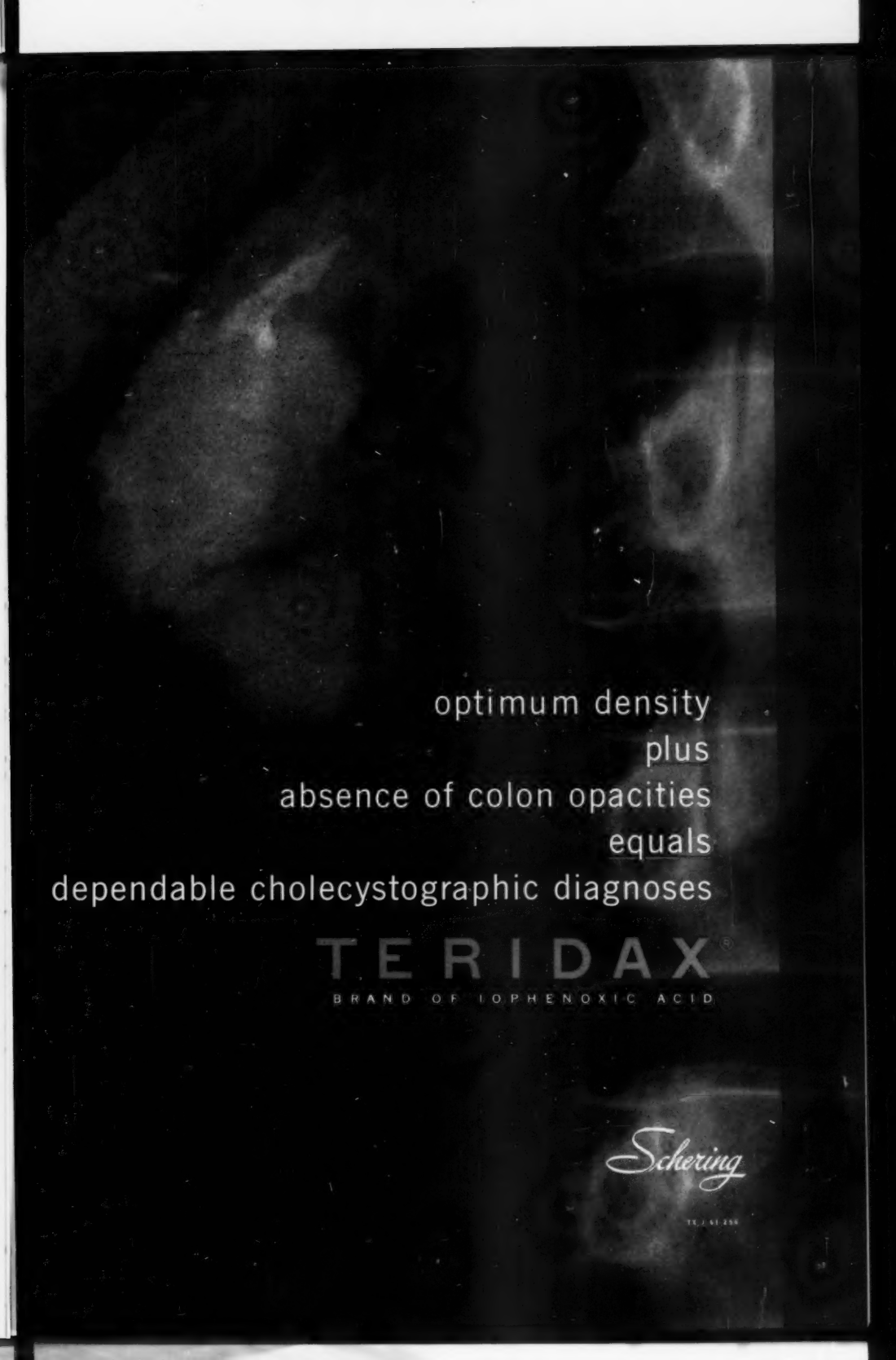
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VOLUME 26 AUGUST, 1956 NUMBER 2

ACUTE GASTRITIS AS THE CAUSE OF OTHERWISE UNEXPLAINED UPPER GASTROINTESTINAL HEMORRHAGE*

E. LEONARD POSEY, JR., M.D., F.A.C.G.

and

SAMUEL L. STEPHENSON, JR., M.D.

Jackson, Miss.

A host of disease states capable of producing hemorrhage from the upper gastrointestinal tract have been long recognized and categorized. The most exhaustive classification available is that of Smithies[1] (Table I). In evaluating

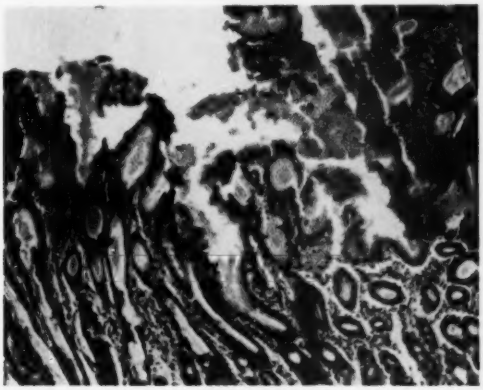

Fig. 1a

any given case presenting hematemesis and/or melena, the clinician must, for the sake of diagnostic accuracy, remind himself of the more exotic situations as well as those more commonly encountered.

*Presented before the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, Chicago, Ill., 27, 28, 29 October 1955.

From the Veterans Administration Center, the University of Mississippi School of Medicine, and the Posey-Stephenson Clinic, Jackson, Miss.

Faced by such a formidable array of diseases, one may take solace in certain statistics which have been compiled. In 668 cases of upper gastrointestinal bleeding studied by Rivers and Wilbur[2], intrinsic gastroduodenal disease was responsible for 90.3 per cent, cirrhosis and portal hypertension for 5.1 per cent, while all other causes accounted for only 4.6 per cent.

TABLE I

(After Smithies)

Gastrorrhagia is associated with hematemesis, or melena, or both as follows:

1. In primary gastric disease, acute or chronic gastritis, simple or phlegmonous, acute gastric erosion, acute or chronic benign ulcer, *ulcus carcinomatosum*, carcinoma, sarcoma, syphiloma, tuberculoma, polyposis, ulcerated gastric cirrhosis, varicosities, or aneurysm of intrinsic gastric arteries or intramural parasite (echinococcus nematodes).
2. In conjunction with chronic disease of the heart or blood vessels.
3. Complicating disease of the liver, gallbladder or ducts, (cirrhosis, neoplasm, portal thrombosis, Banti's disease, cholelithiasis, cholecystitis).
4. Disease of the spleen (chronic splenitis, leukemia, Gaucher's spleen).
5. Malfunction of the pancreas (acute and chronic pancreatitis).
6. Toxemias associated with ailments of the kidney, central nervous system, thyroid gland, adrenal, hemolymph nodes.
7. Bacteremias and protozoemias (typhoid fever, smallpox, measles, malaria, yellow fever, cholera).
8. Chemical poisons and probably following burns of the body surface.
9. Local injury (a) Trauma from falls, foreign bodies, blows, crushing injuries or stab wounds; (b) poisons introduced by mouth.
10. Disordered blood states: Hemophilia, purpura, chronic anemia, acute or chronic cholemia (to which should be added anticoagulant poisoning; e.g., Heparin, Dicoumarol—Authors).
11. In conjunction with certain neuropathic states as hysteria, angioneurotic edema, tabetic crises, epilepsy, progressive paralysis.
12. In association with physiologic cycles of females, as the catamenia and climacteric.
13. Following operations upon organs other than the stomach, particularly when such operations are intraperitoneal.
14. Blood may enter the stomach from a diseased lung, esophagus, adjacent viscus (duodenum, jejunum or colon by fistula) or great vessel.

MacBryde's[3] findings are similar. He found peptic ulcer in 52.9 per cent, hepatic cirrhosis with ruptured esophageal varices in 12.5 per cent, gastric carcinoma in 2.3 per cent, hiatal hernia in 2.1 per cent, gastritis and gastric erosions in 1.1 per cent, ruptured aortic aneurysm in 0.8 per cent, miscellaneous 7.5 per cent, while the source of bleeding was undetermined in 20.6 per cent.

In considering gastritis as an etiological factor in upper gastrointestinal hemorrhage, one encounters a diversity of opinion. No case of gastritis is listed by Schear, Bowers, and Sullivan[4] in their recent study. MacBryde[3] found gastritis in 1.1 per cent of his cases. On the other hand, E. D. Palmer[5] found hypertrophic gastritis in 19 of 121 instances of bleeding. Dagradi, Sanders, and Stempien[6] found hemorrhagic gastritis present in 27 of 62 cirrhotics with hemorrhage, virtually as many as bled from varices! Gott et al[7] encountered gastritis in 5.1 per cent of 195 cases of severe bleeding.

Benedict[8] has long emphasized the propensity of gastritis to bleed. Of his 213 cases, 19.7 per cent hemorrhaged. According to Schindler[9], at least 10 per cent of patients with gastritis bleed. Of 165 instances of hypertrophic gastritis seen by E. D. Palmer[5], 12 bled as the initial manifestation of the

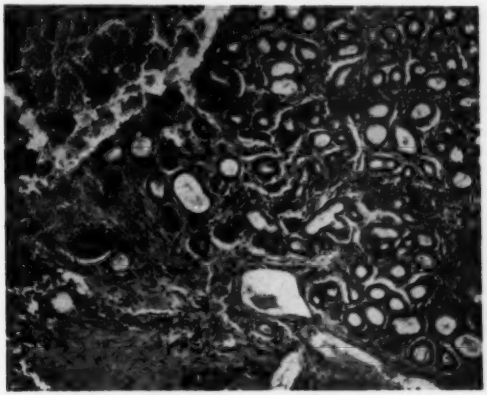

Fig. 1b

disease. Hemorrhage was encountered in 20 per cent of the series collected by Fieber[10].

The present report represents an attempt to summarize our personal experience dealing with gastritis and bleeding over a five-year period in a single institution.

Method of Study

All cases of upper gastrointestinal hemorrhage seen at the Veterans Administration Center, Jackson, Miss. from June 1949 through May 1954 were reviewed. The diagnoses were tabulated to determine the incidence of each disease encountered. All cases of gastritis established by gastroscopy and/or surgery were carefully studied to determine the clinical picture, the severity of bleeding, and the importance of possible etiologic factors. The records of all gastroscopies performed during this interval were reviewed to determine the incidence and types of gastritis seen and to ascertain the frequency of

hemorrhage in this group. X-ray evidence of gastritis was noted, but was not considered diagnostic unless gastroscopic or surgical confirmation was obtained. Detailed attention was given only to those instances of acceptable gastritis in which no other likely factor was present to account for bleeding.

Results of Study

1. *Entire series:*—All patients were males. This is without significance since in excess of 99 per cent of individuals admitted to this hospital are males. No significant difference was observed in the incidence of the various diseases between the white and negro races. Approximately equal numbers of whites and negroes were admitted.

TABLE II

Causes of Upper Gastrointestinal Hemorrhage in Present Series

Diagnosis	Number	Percentage
Duodenal Ulcer	104	68.9
Bleeding from Esophageal Varices	10	6.6
Acute Gastritis	7	4.6
Gastric Ulcer	4	3.8
Hiatal Hernia	3	2.1
Gastric Carcinoma	2	1.4
Esophageal Carcinoma	1	0.7
Portal Vein Thrombosis	1	0.7
Posttraumatic Gastric Hemorrhage	1	0.7
Jejunitis	1	0.7
Undetermined	14	9.3
Total	148	100

The various conditions encountered in the total group of 148 cases are presented in Table II. It should be noted that these individuals are listed as patients with one or more than one diagnosis rather than as separate admissions for different disorders. The usual preponderance of cases in the duodenal ulcer category was found (104), while bleeding esophageal varices (10), gastritis (7), miscellaneous conditions (13), and the undetermined group (14), are in the distinct minority. Intrinsic gastroduodenal disease was discovered in 122 instances.

The overall mortality for the entire series was 25 (13.8 per cent). The various lethal conditions are shown in Table III. It will be observed that the

more grave conditions were accompanied by the greatest death rate. The low incidence among the duodenal ulcer category (4 deaths) with no postoperative deaths deserves emphasis. It should also be stressed that no fatalities eventuated among the group with gastritis.

Fifty-one of these patients (33.4 per cent) were admitted on two or more occasions. More than one condition potentially capable of producing hemorrhage was discovered in 11 individuals (7.3 per cent) as tabulated in Table IV. The obvious or the more likely diagnosis was given as the cause of bleeding in each instance.

X-ray evidence of gastritis, consisting of thickening and irregularity of the mucosal folds of the stomach, usually associated with irritability and spasm, was observed 46 times. A positive x-ray was obtained in only 3 of the 7

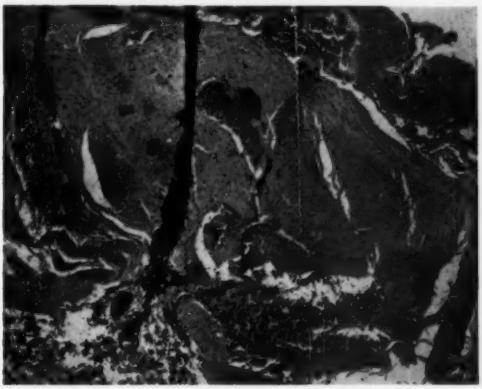

Fig. 1c

gastritis patients who bled. In 43 of the duodenal ulcer group x-ray changes "typical of gastritis" were noted. Only 12 of these cases were subjected to gastroscopy; in 4 the diagnosis was corroborated; in 8 a normal mucosa was seen.

2. *Gastritis:*— The Schindler[9] classification of the gastritides is uniformly employed throughout this study.

During the five-year period under consideration, 478 patients were subjected to gastroscopy. In 116 instances (24.8 per cent) some form of gastritis with or without additional pathology was visualized (Table V). Bleeding occurred in 7 of these individuals, giving an incidence of 6.9 per cent. These 7 patients were admitted for a total of 11 admissions because of hemorrhage. The pertinent data is summarized in Table VI.

Age:—These seven varied from 29 to 44 years of age with an average age of 35.6 years at the time of hemorrhage. This is at least partly due to the fact that each was a veteran of World War II.

Seasonal incidence:—By far the most common time of bleeding was in the late fall and winter months. All but one admission were encompassed by the period between September and March. A single admission occurred in June.

Mode of onset of hemorrhage:—In 8 admissions of 5 patients, the bleeding appeared suddenly and dramatically with the unheralded appearance of hematemesis followed by melena in 5 instances, hematemesis and melena in 2, and hematemesis with bright blood per rectum in 1. The picture gradually and slowly developed in 3 admissions, appearing as melena only in 2 instances, and melena followed after one week by sudden hematemesis in 1 instance. Of the 3 patients with recurrent bleeding, the initial pattern was repeated in

TABLE III

MORTALITY IN PRESENT SERIES

	Total Number Of Cases	Number Died
Duodenal Ulcer:		
Medical Management	80	4
Surgical Management	24	0
Undetermined	14	8
Bleeding Esophageal Varices	10	7
Gastric Carcinoma	2	2
Esophageal Carcinoma	1	1
Portal Vein Thrombosis	1	1
Posttraumatic Gastric Hemorrhage	1	1
Gastric Ulcer	4	1
Total	137	25

2 (sudden onset) and varied in 1 (sudden, the initial blood loss developed gradually).

Premonitory symptoms:—In only one instance was there any preceding dyspepsia prior to bleeding. All patients with recurrent hemorrhage denied interim indigestion.

Severity of hemorrhage:—Bleeding was marked in only two admissions. In each instance, shock was present. The admission hemoglobin was 8.2 and 8 grams respectively. In one of these, 10 pints of blood were required prior to gastric resection, and an additional 5 pints were necessary in the immediate postoperative period! In the other, 4 pints of blood were administered. Blood loss was moderate in 6 admissions. The initial hemoglobin ranged from 10.0 to 11.5 gm. in this group. One of these was given 2 pints of blood, 2 were

given 1 pint. In the remaining 3 admissions, blood loss was mild; the initial hemoglobin was 12 gm. or over; no transfusion was required.

Gastric analysis:—Free acid was found in the fasting gastric contents of every admission. The majority of these determinations were made at gastroscopy following gastric evacuation with the Ewald tube. Titration was not carried out.

Roentgen findings:—Gastrointestinal x-ray studies were carried out as soon as bleeding ceased in each admission. Gastritis was suggested in 3 instances. No abnormalities were disclosed in 8 examinations.

Gastroscopic findings:—Superficial gastritis was encountered in 5 admissions. Of these, 2 presented actual erosions and active bleeding. Hypertrophic gastritis was disclosed in 6 admissions, with erosions being seen in 3 instances. The patients were referred to gastroscopy from 7 to 12 days following hospitalization and had been rendered vigorous therapy prior to examination. Patients with recurrent bleeding were found to have the same type of gastritis on subsequent studies.

TABLE IV

MULTIPLE CONDITIONS ENCOUNTERED

Primary Diagnosis	Number	Secondary Diagnosis	Number
Duodenal Ulcer	4	Gastritis	4
Duodenal Ulcer	3	Duodenal Diverticulum	3
Duodenal Ulcer	2	Hiatal Hernia	2
Gastric Ulcer	1	Duodenal Ulcer	1
Esophageal Varices	1	Duodenal Diverticulum	1

Mortality:—No death eventuated in this series.

Surgery:—Subtotal gastric resection for uncontrolled bleeding was required in a single instance. Severe hemorrhagic gastritis was found in the surgical specimen (Fig. 1).

Length of hospitalization:—The briefest period of hospital confinement was 6 days; the longest was 53 days (the patient requiring surgery). The average stay was 16.4 days.

Possible etiologic factors:—Each record was carefully examined for evidence of any agent potentially capable of initiating a gastritic reaction. In 9 of the 11 admissions, bleeding developed either during or immediately after (within 72 hours) an alcoholic debauch. In a single patient a possible sensi-

tivity to orange juice was noted; each of 2 hemorrhages followed ingesting large quantities of this beverage. This patient alleged to have bled on 6 other occasions after drinking orange juice; he denied interim exposure to orange in any form.

Medical management:—Since several ward physicians cared for these patients, the therapeutic program varied somewhat in its details. In general, treatment consisted of replacement with whole blood when indicated, the early institution of modified Meulengracht feedings with antacids and antisecretory drugs on a 24-hour basis, barbiturates and, when necessary, narcotics.

Comment

Our experience corroborates that of others, that acute gastritis is a not infrequent cause of gastrointestinal hemorrhage, that it may induce a severe loss of blood and that, rarely, surgical intervention may be required to halt exsanguination. We feel that the possibility should be routinely entertained in the differential diagnosis of every case. A detailed anamnesis, a careful and complete physical examination, the ascertaining of the blood coagulation factors (coagulation + bleeding times, prothrombin time, fibrinogen index, platelet count), the determination of capillary fragility, cautious roentgen studies as soon as bleeding is controlled[11], followed when indicated by early esophagoscopic and gastroscopic examinations[12] will result in a diagnostic accuracy in the overwhelming majority of cases. This plan, employed routinely by us in our private practice, has enabled us to determine the site of bleeding in every case of upper gastrointestinal hemorrhage seen in the past six years.

TABLE V

Types of Gastritis Found in 478 Gastroscopies 1949-1954

Type	Number
Hypertrophic Gastritis	82
Superficial Gastritis	10
Atrophic Gastritis	4
Mixed	5
Postoperative Gastritis	5
Carcinoma with Atrophic Gastritis	4
Gastric Ulcer with Hypertrophic Gastritis	5
Gastric Polyp with Hypertrophic Gastritis	1
Total	116

TABLE VI

GASTRITIS

Patient	Days of Hosp. Stay	Age	Date	Dyspepsia	Mode of Onset	Shock	Hb. (gm.)	Transfusions Pints	Free HCl	G.I.	Gastroscopy	Possible Etiology
Kir.	13	42	Dec. 1949	No	Slow	No	12	None	Pos.	Neg.*	S.G.† (Erosions)	Alcohol
	53 (Surgery)		Mar. 1950	No	Sudden	Yes	8	15	Pos.	Pos.	S.G. (Erosions)	Alcohol
No	16	29	Jan. 1953	No	Sudden	No	11.5	2	Pos.	Pos.	H.G.‡ (Erosions)	Alcohol
Hu	19	34	Oct. 1952	No	Sudden	Yes	8	4	Pos.	Neg.	H.G. (Erosions)	Alcohol
Sm	7	36	Dec. 1949	No	Sudden	No	12.5	None	Pos.	Neg.	S.G.	Alcohol
	6		Jan. 1950	No	Sudden	No	13	None	Pos.	Neg.	S.G.	Alcohol
	13		Mar. 1950	No	Sudden	No	11.5	None	Pos.	Neg.	S.G.	Alcohol
Ma	11	35	Feb. 1954	2 Wks.	Slow	No	11	None	Pos.	Pos.	H.G.	Alcohol
Gr	23	32	Sept. 1953	No	Sudden	No	10	2	Pos.	Neg.	H.G.	Orange Juice
	10		June 1954	No	Sudden	No	11.5	None	Pos.	Neg.	H.G.	Orange Juice
He	10	44	Jan. 1951	No	Slow	No	11	1	Pos.	Neg.	H.G. (Erosions)	Alcohol

*X-ray read positive or negative for gastritis
†Superficial gastritis
‡Hypertrophic gastritis

We consider the demonstration of alcohol as an etiologic or precipitating factor to be one of our most significant findings. Although no complete unanimity of opinion exists on the subject, most workers question that alcohol is of importance in this problem. Fieber[10] concedes that allergy may play a role in the genesis of gastritis, as may emotional factors of inheritance, but he sees no correlation with exposure to alcohol or nicotine or with vitamin deficiencies. E. D. Palmer[13] denies that alcoholic consumption can produce *chronic* gastritis. He fully subscribes to the idea, however, that large amounts of alcohol ingested over a brief period may result in a clinically and pathologically significant form of gastritis. Of 100 severe alcoholics of long standing studied gastroscopically by Berry[14], 30 per cent present a normal mucosa, 35 per cent had mild superficial gastritis, and only 35 per cent had unequivocal chronic gastritis. Whether or not any of these individuals had a history of bleeding was not stated. The work of Gray and Schindler[15] should also be recalled. Of 100 severe chronic alcoholics studied by them, 55 per cent had normal mucosae, 45 per cent presented superficial or atrophic gastritis or both; mucosal hemorrhages were visualized in 22 per cent. There was no correlation between the occurrence or the severity of the gastritis and the duration or the severity of the alcoholism. We must conclude that alcohol, consumed in large quantities over a brief span of time may, in certain predisposed individuals, act as an exogenous irritant and initiate an acute gastritic reaction of sufficient severity to cause hemorrhage. The place of alcohol in the genesis of chronic gastritis is outside the scope of this report.

It is important to realize that these seven individuals bled as the *initial* manifestation of their gastritis. No other hemorrhage was encountered in the 109 remaining cases of gastroscopically proven chronic gastritis diagnosed by us during this five-year period. All of these 109 cases had gastrointestinal complaints of more or less chronic nature. None of the bleeding cases had interim symptomatology. Twelve of E. D. Palmer's 165 cases of hypertrophic gastritis bled as the first manifestation of their disease[5]. We feel that acute gastritis with hemorrhage behaves in a different manner from chronic gastritis and is, in effect, a different disease entirely. The exogenous agent, be it alcohol or an allergen (as in the patient with supposed sensitivity to orange juice) apparently produces a sudden violent mucosal reaction with congestion, erosion, and hemorrhage, which heals without residual symptoms with a few days time. Follow-up gastroscopic studies in such cases would be of considerable value.

The fact that those patients having more than one admission showed the same type of gastritis on subsequent examinations is most interesting. This would seem to indicate that each individual gastric mucosa reacts after acute exposure to exogenous offenders in a characteristic manner. Apparently the response is not predetermined by the precipitating agent; both superficial and

hypertrophic gastritis were seen in different patients to result from the same factor, alcohol.

The absence of mortality in the gastritic bleeding group is in sharp contradistinction to that seen in the other categories. A survey of the literature has failed to uncover a single reported case of fatal hemorrhage from gastritis. Apparently this condition is essentially a benign disorder even though blood loss may be profound.

We are fully cognizant that the lack of gastroscopic biopsy material in this series removes it from the ideal. The failure of the visualized abnormalities to correlate with microscopic examination of the biopsy specimens has been satisfactorily documented by many workers[10,16,17]. E. D. Palmer[13], in the most exhaustive critique available on the subject is most emphatic in this regard. He offers a complete classification of the gastritides based on pathologic criteria which may at least partly supplant that of Schindler[9] which derives from the gastroscopic picture. The five admissions in which erosions and bleeding were visualized provide ample proof that bona fide damage was present. This cannot be stated for the remaining six admissions. Our contention, however, that true pathology existed is strengthened by the fact that careful study failed to disclose any other condition which could be responsible for the bleeding.

The failure to correlate x-ray changes interpreted as due to gastritis with the gastroscopic appearance of the stomach deserves emphasis. Whether alterations of the *muscularis mucosae* is responsible for the roentgen changes cannot be stated. We feel, however, that one is never safe in assuming the presence of gastritis on the basis of x-ray examination alone. Endoscopic study, preferably with biopsy, is essential to the establishment of an accurate diagnosis.

One should not conclude from this study that the chronic gastritides are immune from bleeding. Although no example was encountered in our series, we have seen several such cases in our private practice, as have others[1,3,5,7-10,18,19].

In the careful examination of any sizeable group of bleeders, more than one condition potentially capable of causing hemorrhage will frequently be encountered[20]. Such a situation existed in 7.3 per cent of our total series. We feel that gastritis, when found, should not be considered as other than an incidental factor unless actual erosions are visualized or unless bleeding from the other pathologic conditions present can be excluded with certainty. From a statistical point of view, gastritic hemorrhage will be present in from 5 to 10 per cent of cases. There is no characteristic clinical picture associated with this disorder. One should therefore remind himself of the possibility of the

condition and proceed to search for it in a logical and sequential manner in order definitely to establish the diagnosis.

Summary and Conclusions

1. Seven patients with upper gastrointestinal hemorrhage due to gastritis alone were encountered in a series of 148 cases. These seven patients were seen for a total of 11 admissions over a five-year period. Bleeding occurred most frequently in the late fall and winter months. Blood loss was severe in two admissions, mild or moderate in nine. In a single instance subtotal gastric resection was required to stop the bleeding. The average hospital stay was 16.7 days. Free hydrochloric acid was demonstrated in the gastric contents of each patient.

2. In every patient, bleeding was the initial manifestation of the gastritis. There was no interim or premonitory dyspepsia other than two weeks of vague symptoms in one patient. In 8 admissions bleeding appeared dramatically; in 3 it developed slowly.

3. In 6 patients, bleeding followed within 72 hours the excessive imbibing of alcohol. In 1 patient, repeated bleeding followed ingestion of large amounts of orange juice.

4. The clinical differences between this group and a group of 109 cases of chronic gastritis seen during the same period are discussed.

5. No fatality occurred in this series.

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MASSIVE HEMATEMESIS WITHOUT GROSS LESION*

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Massive upper gastrointestinal hemorrhage is always a challenging problem to the clinician but not infrequently is also a cause of great concern to the pathologist who is to explain the mechanism of hemorrhage or demonstrate an anatomic cause. We have been impressed for some time by our inability to demonstrate an anatomic cause in some cases of massive hemorrhage. Furthermore, the literature gives evidence that many others have had the same problem. From some of the larger cities and their hospitals come reports citing "hemorrhage of undetermined origin" in nearly one-quarter of their cases[1-4] while a figure up to ten per cent is not at all unusual[5,6]. Much higher figures are given in other reports[7-9].

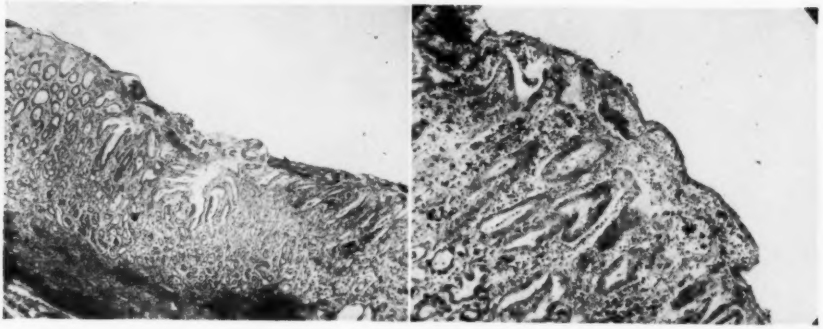

Fig. 1 Fig. 2

Fig. 1—Tiny superficial bleeding, erosion covered chiefly by fibrin.

Fig. 2—Higher magnification showing red blood cells, fibrin and surface pseudoepithelial membrane.

For material of this report we have selected the cases of "no anatomic cause" from the Milwaukee County Hospital and the Veterans Hospital, Wood, Wisc. We have excluded all cases of: a. peptic ulcer history, b. suggestive or positive x-ray findings, c. anatomic lesion found by the surgeon, d. finding of ulcer by pathologist, and e. all cases having some other primary illness, such as, intracranial disease, cirrhosis of the liver, lobar pneumonia, uremia, and blood dyscrasias. The material, therefore, is limited to cases of upper gastrointestinal hemorrhage in otherwise good health whose stomach was avail-

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able for study either as a surgical or autopsy specimen. The problem then is to explain the clinical finding of hemorrhage on an anatomic basis.

It is quite reasonable to assume that massive bleeding from the stomach should have an anatomic lesion. Our attention was brought into sharp focus by the case of a 27-year-old female who suddenly had massive bleeding from the stomach without any finding. An emperic gastric resection was performed and no ulcer was found either by the surgeon or pathologist. On the posterior wall, however, near the lesser curvature in the midportion of the stomach a very light reddish tan 2 mm. area was observed. The pattern of the gastric mucosa was undisturbed. This was presumed to be a minor hemorrhage in the mucosa due to surgical manipulation. Section was taken of this area and on microscopic examination an acute ulcer was discovered. The ulcer involved the submucosa and measured 3 mm. in diameter but the mucosal edge of the

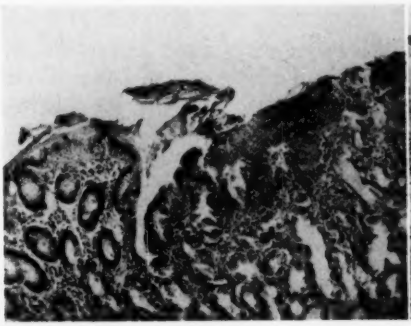

Fig. 3

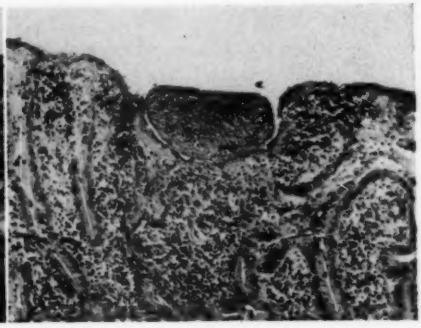

Fig. 4

Fig. 3—High-power view showing pseudoepithelial membrane on the left side and erosion with fibrin covering on the right side.
Fig. 4—Dense fibrin plug occupying superficial erosion.

ulcer was overhanging and in the direct center was a mass of fibrin. The ulceration was not recognized because the area was filled with fibrin and the mucosal surface pattern was not sufficiently changed to arouse any suspicion on the part of the examiner. With this in mind subsequent gastric specimens were specifically examined and all old material was re-examined.

This study has shown that very minute and frequently very superficial mucosal erosions are present in the great majority of the specimens originally called "chronic gastritis" or "without anatomic change". The reason for failure to identify such erosions grossly lies in the fact that many of them are covered by a layer of fibrin in which the dimpled mucosal pattern and its color are not sufficiently altered to arouse suspicion. This early fibrin deposition may also have some relationship to the presence of a pseudoepithelial layer on the surface of the mucosa as reported by Jorda[12]. The sequence of events leading

to this phenomenon will be shown by means of photographs (Figs. 1-4). A second reason for failure to identify erosions which are deep lies in the fact that many of these mucosal ulcerations are also covered or the defect is filled by a combination of fibrin and false membrane. For some reason erosions commonly begin in the furrows of the gastric mucosa and are not readily seen. That more of such erosions have not been appreciated apparently lies in the lack of sufficient numbers of histologic sections. These microscopic and near microscopic erosions occur primarily in stomachs which otherwise are designated as those of hypertrophic gastritis. We have encountered only one case in an atrophic mucous membrane. The distribution of such erosions cannot be accurately stated although there is a strong suggestion that many of them are located in the area of the lesser curvature. Males are predominant in the series and the age distribution has a peak in the fourth and fifth decades.

Conclusions

The great majority of our cases of massive upper gastrointestinal hemorrhage without gross anatomic lesion have shown the presence of superficial erosions. These erosions are not detected grossly because of filling of the defect by fibrin layer. The pseudoepithelial layer of the stomach may play an important part in developing a surface membrane which fills zones of erosion. The cause of the gastric erosions has not been determined.

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PHYSIOLOGIC EFFECTS OF GASTROINTESTINAL HEMORRHAGE*

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Rate and extent of bleeding are prognostic variables inherent in all instances of hemorrhage. But it is clear that the physiologic toll of bleeding is more or less proportional to the pre-existing status of various body mechanisms, for as each is called upon to exert its compensatory reaction to the bleeding, it either succeeds or fails to respond in accordance with its functional ability. Even after blood replacement and an apparently successful response to the exigencies of diminished blood volume, an organ or functional system may fail to return to a normal status.

This situation appears to apply particularly to gastrointestinal bleeding for two main reasons. First, gastrointestinal hemorrhage is prone to result in irreversible shock earlier than does peripheral bleeding of comparable volume. Second, the age group in which gastrointestinal hemorrhage occurs is preponderantly that in which associated infirmities of the cardiovascular, renal, and hepatic organs are prominent. If blood is lost slowly enough, the clinical problem is no longer one of hemorrhage, but of anemia.

In this review the known physiologic effects of gastrointestinal hemorrhage are delineated in relation to the various systems. The cardiovascular system, in its antagonal responses to the effects of hypotension, tachycardia and diminished blood volume, is subject to such consequences as acute coronary occlusion, peripheral arterial occlusion, and phlebothrombosis.

The renal system, by virtue of its remarkable participation in vasoconstrictive phenomena, may exhibit posthemorrhagic renal insufficiency. Absorption in large amounts from blood in the bowel at a time when renal clearance is hampered by a diminished volume-flow of blood, results in azotemia. This extrarenal azotemia is almost entirely accounted for by a rise in blood urea, and because creatinine and uric acid levels are normal, it can be differentiated from uremic states. Actually the blood urea level has been utilized as a prognostic sign in gastrointestinal bleeding.

Hepatic effects are exemplified by the physiologic aberrations associated with cirrhosis, and the consequent poor tolerance of massive bleeding.

Variations in blood chemistry pursuant to bleeding are largely dependent upon the state of hydration in relation to effective circulating blood volume. Massive blood replacement may affect clotting mechanism by causing thrombopenia.

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Wound healing is notoriously poor following massive gastrointestinal hemorrhage. If bleeding has continued massively for more than 48 hours, replenishment of the original hematologic and chemistry values does not necessarily reflect those of the tissues. The lag in tissue protein anabolism is not always reflected in blood values.

It is against these features of gastrointestinal bleeding that the physician and surgeon must calculate risk in their judgment of therapy.

Discussion

Dr. I. Snapper (Brooklyn, N. Y.):—Both the papers by Drs. Posey and Stephenson and Dr. Kuzma have emphasized the importance of the problem of gastric or upper intestinal hemorrhage.

Teams have been formed in large hospitals which take special care of the patients who come in with gastrointestinal hemorrhage, and figures are quoted that, unless such teams are available, the fatality from gastrointestinal hemorrhage may go up to astronomical figures of 10 to 20 per cent. As far as facts and figures are concerned, it is certain that before 1927, the overall fatality of all gastrointestinal hemorrhage was not above 2 per cent. These old statistics have been compiled so carefully that this figure cannot be doubted.

Are there any new developments which could explain the high fatality figures for gastric hemorrhage in our modern hospitals?

During the years 1926-1927, blood transfusion became a routine treatment. We have, therefore, to consider the paradox whether blood transfusion which was introduced in order to save lives could be the reason why the fatalities of upper intestinal hemorrhages have soared. In general a hemorrhage stops when a clot forms in a blood vessel. The obturating clot remains in place because during the hemorrhage the circulating blood volume decreases.

We know for certain that increase of the circulating blood volume increases the tendency to hemorrhage. This we learned the hard way during the treatment of the hypoproteinemia which, at least partly, is the cause of ascites in liver cirrhosis. When a patient who has liver cirrhosis, ascites, and hypoproteinemia, receives human albumin intravenously, the serum albumin increases and the tendency to ascites formation must become less marked. Notwithstanding the sound principle which underlies this treatment, intravenous injections of human albumin are no longer given to patients with liver cirrhosis. This method had to be abandoned because the added albumin attracted water, and the circulating blood volume increased. The increase of circulating blood volume in patients with liver cirrhosis and varicosities of the esophagus was sufficient to cause serious, often fatal, esophageal hemorrhages. Therefore, the decrease of the circulating blood volume which takes place during a hemorrhage must be an important factor in the cessation of the

bleeding. This reduction of the circulating blood volume should not go too far. If it goes too far, then the peripheral circulation becomes impossible and collapse ensues. To prevent the dangerous collapse due to excessive reduction of the circulating blood volume, blood transfusion is an excellent method.

If a patient with upper intestinal hemorrhage goes into collapse, has a rapid pulse, is sweating, then a blood transfusion is indicated. Such a blood transfusion should never aim to bring the circulating blood volume back to normal. To expedite the cessation of the hemorrhage, the circulating blood volume should remain smaller than normal, although not so small that collapse results. Therefore, only moderate quantities of blood should be given, sufficient to bring the patient out of collapse.

Our "teams" in large hospitals adhere to an entirely different concept. Their intention is to transfuse the patient until the blood pressure is back to normal and the hemoglobin has risen to at least 10 gm. per cent. It is quite evident that such lavish transfusions increase the circulating blood volume to normal and prevent the hemorrhage from stopping. This must explain why the classical fatality of 2 per cent for gastric hemorrhages has gone up in modern hospitals to discouragingly high levels. In my opinion it is probable that the modern treatment of upper gastrointestinal hemorrhage by our hospital teams often favors continuation of hemorrhage.

I am deeply interested in one of the illustrations Dr. Kuzma has shown. The surgeons always try to frighten us by depicting a large artery which sticks out like a steam stack in the middle of the stomach and squirts blood like a geyser. Of course, this frightening picture must occasionally occur. Much more frequent is the extensive hemorrhage due to oozing from tiny blood vessels!

The problem of gastritis seems to be different in different parts of the world. If I understood our speaker correctly, he does not see too much connection between ulcers and gastritis. One obtains the impression that in certain areas gastritis is usually alcoholic in origin and does not lead to ulcers. In other areas where gastritis is hardly ever alcoholic in origin, gastritis frequently seems to be followed by ulcer formation.

Dr. Owen H. Wagensteen (Minneapolis, Minn.): It is hard to know what to say about all this. Every once in a while one gets the impression that a certain therapeutic principle has become firmly established and fixed in general usage. Then suddenly, we hear a voice from the past which you think is incapable of being resurrected; it comes up and blows Gabriel's horn and toots an old tune, which most of us had come to reject.

Publicly, I want to express my keen admiration for my great friend, Dr. Snapper. I must confess, however, I would find it a bit difficult to follow him in what he says about the management of massive gastric hemorrhage.

You know and I know that we cannot resolve this difficult problem from a lecture platform. Dialectics is not that good a remedy for anything.

As Dr. Laufman said in his concluding sentence, it is difficult even with test cases, unless one had a large series of test cases which met the criteria of the test, to arrive at what is best to do. Age, obesity and physical disability and a host of factors bear upon the issue and make a big difference. To construct a crucial hurdle which will permit of careful scrutiny of the evidence and produce a decision which is acceptable to all of us is not easy.

If anyone is not persuaded of the value of transfusions in gastric hemorrhage, one might very well ask whether he would use this agency in hemorrhage elsewhere? When one knows that fibrin clots which may temporarily staunch the hemorrhage are washed away again by the flow of gastric juice, this occurrence magnifies the complexity of the problem many fold, when one is dealing with acid-peptic secretion and hemorrhage. One transfuses in hemorrhage in part to allay the systemic effects of loss of blood. A surgeon, when he is faced with the problem of hemorrhage in a wound may resolve now and then to leave the patient to his own resources, believing that as shock supervenes the hemorrhage will stop. I think the majority of us feel, from experience, that such a procedure is a poor alternative.

Dr. Snapper told us that it would be impossible for me to change his mind, and I think the majority of you agree with me. So, why say more? (Laughter) A lawyer can destroy his own case by talking too much and too long.

Now, not far from here, in Mackinac Island, William Beaumont took care of Alexis St. Martin, long before the days of formal operative surgery, and had the opportunity, through a day-to-day gastroscopy made possible by a large gastrostomy opening, to see what happened in Alexis' stomach. St. Martin was addicted to the use of alcohol. William Beaumont reported 122 years ago, in the classical paper published in Plattsburg, New York, in 1833, the presence of hemorrhages following the ingestion of alcohol.

I suspect that if Dr. Berry were to peer into the stomachs of a number of this audience tonight, who might justifiably upon conclusion of this long program imbibe two or three cocktails upon empty stomachs, he probably would see some of the hemorrhagic erosions that William Beaumont described. Fortunately, alcohol has a stimulating effect on the appetite for most people. One is driven to go to the dining room to eat, and the reparative process begins directly.

I was very much interested in Dr. Kuzma's beautiful presentation. I have never seen the origin of these erosions as nicely shown as he traced them for us today. I would like to have him tell us a little more about how he got this material, whether these were surgical specimens, etc.

Most of you know that Professor Florey (now Sir Howard), before he became involved in the development and manufacture of antibiotics was very much interested in the secretion of mucus from segments of the alimentary tract. He found you could exhaust the mucus within the glands of the colon with an hour's stimulation of the parasympathetic nervous system. In this period of time there was no loss either of the surface gastric mucus or of the mucus in the gland crypts. I have come to think of that superficial layer which Dr. Kuzma showed us as a sort of carpet—a velvety carpet of mucus. He, perhaps, has tested this secretion with chemical stains to identify it. In any case, he gave it a somewhat different name. Sir Howard could not even get rid of the surface mucus, let alone the mucus down in the cells.

One of my former associates, Dr. Enrique Sanchez, now in Mexico City, a number of years ago spent a good deal of time on this study. He used local mucolytic agents, as well as parasympathetic stimulation. He kept a constant vigil over some of the dogs over a 96-hour interval, keeping the dog under anesthesia, with a catheter in the bladder, and kept the dog warm. He failed, over a 96-hour period of continuing stimulation, to exhaust the mucus-secreting capacity of the gastric mucous glands. By giving histamine and mucolytic agents, he could get rid of the surface layer of mucus which Dr. Kuzma showed us, but he could not exhaust the capacity of the glands to secrete.

This morning I said that in the gastric juice resides the cause of duodenal ulcer. One needs only to drip that juice onto the esophageal mucosa of a cat. If one drips gastric juice from a patient who has no ulcer—even though the pH is adjusted to 1.6, one rarely observes any evidence of digestion of the wall of the esophagus, and so similarly with the juice from the stomachs of patients with gastric ulcer. Dripping such juice rarely causes evidence of esophageal digestion. In other words, the gastric juice plays only a small role—the cause of gastric ulcer probably lies in the greater vulnerability of the gastric mucosa to injury by acid-peptic juice.

During the Revolutionary War period in this country, John Hunter asked himself the rhetorical question: "Why doesn't the stomach digest itself?" Florey failed to find the answer. Enrique Sanchez failed to find the answer. The normal gastric mucosa obviously possesses a great capacity to protect itself from injury by acid-peptic juice. Under certain circumstances, from arteriosclerosis of its blood vessels, from atrophy of certain cellular elements within the mucosa, the capacity of the gastric epithelium to defend itself is lost.

A number of years ago, when I had seen patients die of hemorrhage—from little erosions in the stomach when exploration failed to uncover a cause for the hemorrhage, I persuaded myself—and that is often the most difficult kind of persuasion—that the next time I had a patient upon whom I operated

for massive hematemesis and found nothing, that I would resect the stomach, on the thesis that hematemesis is ordinarily an acid-peptic linked hemorrhage.

In the month of June, 1944, I operated upon two patients in Minnesota, with good Scandinavian names, Henry Johnson and Signe Peterson, in whom we had this sequence of events: massive hemorrhage without response to transfusion; continued bleeding and low blood pressure.

At operation, in the stomach of Henry Johnson, there was nothing to see. I resected the stomach anyway, doing a three-quarter gastric resection, high on the lesser curvature and slightly posterior to the lesser curvature. There was an erosion found in the opened specimen. One could not see or feel it from the outside of the stomach. Neither could the pathologist find it until he opened the specimen.

The next patient had an identical situation. About a month later, one of my associates called me to the operating room for some advice upon a similar situation. He pointed out a hemorrhagic area in the jejunum as the likely cause of the bleeding. I said, "I believe that is only a subserosal hemorrhage without significance." I went down to my office. Later in the day I saw the surgeon and asked him what he did. I had suggested that he should resect the patient's stomach. He said he took out the purpuric spot. The pathologist said that there was some hemorrhage under the serosa.

Five days went by, the patient being transfused meanwhile, 16 times in all. Death occurred on the fifth postoperative day from failure to sustain an adequate blood pressure. At autopsy, when the stomach was opened, an erosion was found in the area described above in the instances of Henry Johnson and Signe Peterson. You can readily understand that my thesis of empirical gastric resection for massive hematemesis won a number of willing converts in our hospital.

So, I would say, when a patient vomits blood, one can write it down that it is in all likelihood an acid-peptic linked phenomenon. In the literature in recent years, there is to be noted a trend to the general adoption of such a program among surgeons.

Rokitansky described these gastric erosions in 1841. For more than a hundred years, these erosions commanded only the interest of the pathologist. But these erosions which Dr. Posey and Dr. Kuzma described can cause death. When there are open vessels in a wound, it is the artery that is the more likely to continue bleeding. When a surgeon employs a rubber drain in an infected wound and hemorrhage occurs from juxtaposition to the blood vessels, it is the heavily coated artery that will give way first. The thin-walled vein lies passively in the wound. The vibrations of the pulsations of the artery against the tube in the infected wound serves to erode the arterial wall, and so similarly in the stomach. That is why patients die of gastric hemorrhage. A small

arteriole is opened. In the presence of acid-peptic juice with strong digestive power and a throbbing, exposed arteriole, the vessel stays open and continues to bleed.

I cannot follow my good friend Dr. Snapper in the idea that bleeding will stop spontaneously. We see failure in other parts of the body of spontaneous arrest of hemorrhage. Regret over neglect is frustrating; experience can be bitter, and suffering is the talisman that tells us: "Next time you have such a situation, don't close your eyes to the situation. Open them. Look and control the situation."

In the State of Minnesota, hemorrhage is the most frequent cause of death from peptic ulcer. I suspect that what is true in Minnesota holds for Illinois and New York as well. One of my associates, Dr. James Casey, has published a study of the causes of death from peptic ulcer in 1952 [Minnesota Med., 37:448-453, (June), 1954]. A number of patients die from hemorrhage before they get to the hospital. They die at home; or they may die in the ambulance on the way to the hospital; they die in the waiting rooms of hospitals before they can be transfused.

If the patient is a good risk, I would strongly urge use of modern day treatment; transfusion, getting the patient to the operating room, and stopping the bleeding as quickly as possible. I think less risk is taken for the patient that way than by waiting.

Dr. Laufman also alluded to the matter of platelets. When you transfuse a patient a number of times, even with fresh blood, you reduce the platelet count which may contribute to the hemorrhage. So, it is important to stop the source of hemorrhage. One patient I transfused 65 times, and then did an emergency resection. That was more than eight years ago, and the patient is alive.

One of the great developments which surgeons are looking toward is growth of knowledge relating to antidiuresis which occurs in patients who have otherwise uncomplicated surgery but exhibit oliguria postoperatively. Following situations such as we have been discussing—protracted hemorrhage followed by operation, urinary suppression is one of the important causes of death. When we solve this problem, the hazard of intervening surgically in some of these patients will be considerably less than it is today.

Question:—I wonder if Dr. Snapper could answer the question: do you think antispasmodic drugs or anticholinergic drugs are contraindicated in bleeding duodenal ulcers?

Dr. Snapper:—The answer is very simple, yes, they are contraindicated because they also prolong bleeding.

Dr. Wagensteen:—How about Dr. Kuzma's slides? I have never seen sections of gastric mucosa tracing the origin of gastric erosions as nice as these. Under what conditions, Dr. Kuzma, did you procure these specimens? Were these surgical or autopsy specimens? What would you regard as a semisquamous membrane? What is its relationship to gastric mucus?

Dr. J. F. Kuzma:—Most of the cases were surgical specimens, which I prefer to handle myself, whenever I can.

I think the best way to examine is to open the stomach on the anterior wall, fix it relatively flat, but with a cotton backing, so that the mucosal surface is a bit convex rather than concave. That opens up the ridges and furrows, and you can get a better look.

Then we fix the stomach in 10 per cent formalin. If we are particularly interested in the Duran-Jorda membrane, we handle the stomach very little and fix it in "formalin" vapor (Formaldehyde). I do not think that is absolutely necessary. After fixation, and under fluid, one takes a hand lens and searches carefully with good light. Then these areas of erosion are a bit easier to pick up because they are a little more dull. They do not have the shininess or the appearance of normal mucosa.

In respect to the membrane itself, I am just beginning to study it. I have no particular opinion at the moment, except that it does not react as mucus does. In that respect, I think I will have to agree with Duran-Jorda, it perhaps is not mucous membrane but some other constitutent which does not have the chemical reaction of normal mucus. What it is, I do not yet know.

Chairman Nix:—Are there any other questions?

Question:—I would like to hear the opinion of Dr. Snapper and Dr. Wangensteen in regard to x-ray, on the basis of patients bleeding mildly and those bleeding severely.

Chairman Nix:—Dr. Wangensteen, would you like to discuss this?

Dr. Wangensteen:—In any problem, it is good to be pre-instructed, if one can be. I am not too much concerned, however, over whether or not a patient has had an x-ray picture. If he is bleeding massively and has vomited blood, I am persuaded that he has an acid-peptic linked source of hemorrhage.

At operation, the first thing one always does beyond examining the duodenum and stomach is to measure the portal venous pressure. A portal venous pressure under 20 cm. of water is normal. A definite increase beyond 30 cm. of water pressure is synonymous with portal hypertension.

If one operates without advices from x-ray films and feels or sees nothing abnormal in the duodenum or stomach, and the portal venous pressure is normal, one knows that portal hypertension is not present, and that an occult gastric or duodenal ulcer and/or erosion is the responsible agent.

If, on the contrary, one is dealing with portal hypertension, one may have a choice of what to do. Drs. Robert Linton, of Boston, and George Crile, of Cleveland, have made an incision in the lower thoracic esophagus and stitched up the varicosities, like one would run an over-and-over suture over an hemorrhoidal vessel in the rectal mucosa.

In my experience with the bleeding of portal hypertension, an ulcer or erosion is found just over the esophagogastric line on the esophageal side; in other words, the source of the hemorrhage is to be found on the esophageal side of the juncture of esophageal and gastric mucosa.

In my experience, in operating for hematemesis from esophageal varices, the choice in such instances would appear to lie between doing something like Drs. Crile and Linton do or excising the terminal esophagus, together with the entire acid-secreting area of the stomach. To make an Eck fistula at such a time would be like teaching a drowning man to swim. I do not know of any surgeon who would perform an Eck fistula for active hemorrhage.

The more likely thing, nine times out of ten, in a situation like this, with massive hemorrhage and hematemesis, is to find a palpable ulcer in the duodenum. If such a patient is found to have a duodenal ulcer, I make a Heineke-Mikulicz duodenotomy and stitch the bleeding off-shoot from the gastroduodenal artery. I then re-oppose the duodenal and antral mucosa to exclude the ulcer crater from further contact with acid-peptic juice, and do a segmental gastric resection, leaving the ulcer. If the bleeding point is dealt with satisfactorily and the defect in the mucosa is closed, the ulcer bed and crater are exteriorized from the alimentary tract, and the risk of subsequent hemorrhage during convalescence is adequately dealt with. To fail to oppose the mucosal surfaces over the ulcer bed would be, I feel, to invite early recurrent bleeding. The adjacent edges of the ulcer crater usually are quite firm and it is a simple matter to approximate the mucosal edges by a few interrupted fine silk sutures.

My answer to the necessity of having x-ray films is, it really does not make a lot of difference, if there has been hematemesis. If hematemesis has not been present, the chances of being wrong are increased considerably. Hematemesis, I feel, means an acid-peptic linked source of bleeding. I have done a total gastrectomy in a patient who did not have hematemesis and who had slight increase of portal pressure to find a couple of years later that my patient had telangiectatic collection of vessels throughout the alimentary tract. This patient had been proctoscoped on numerous occasions in search of such lesions, but they were not seen during life, but were demonstrable at autopsy. If a bleeding patient has an erosion such as Drs. Posey and Kuzma spoke of, I am certain the roentgenologist could not demonstrate them, because such erosions go only to the *muscularis mucosa*. Such lesions have to go down below the *muscularis mucosa* before the roentgenologist can demonstrate their presence.

THE BEHAVIOR OF CARCINOID TUMORS OF THE INTESTINAL TRACT*

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It is a far call from the concept of carcinoid as the innocuous medical curio which was found at the autopsy table in the tip of the appendix to the implications that this tumor holds today. This tumor which arises from the enterochrome system (Kultschitzky cells) is found in the human gastrointestinal tract. It is often called an argentiffinoma. This latter term is derived from the fact that the granules within the cytoplasm often reduce silver. They also give a positive diazo reaction and fluoresce in ultraviolet light. These characteristics are also true of the enterochrome cells which for years were thought, with inadequate proof, to have some neuroendocrine function. The behavior of this tumor may be divided into several aspects: 1. the production of disease by local manifestations in the gastrointestinal tract; 2. its malignant nature and 3. those aspects of it associated with the elaboration of 5-hydroxytryptomine (serotonin enteramine) and perhaps glucogen.

Carcinoid tumors may be found not only in the appendix but in any area of the gastrointestinal tract so that even the stomach and rectum may on occasion be involved. It is estimated that 1 per cent of all gastrointestinal tumors are carcinoids. One form of bronchial adenoma cannot be histologically differentiated from gastrointestinal carcinoid and is for this reason often referred to as a carcinoid type of bronchial adenoma. Whether its cell origin is the same, and whether it elaborates similar substances is not known. The carcinoid tumor usually presents itself as a small nodular mass, the main bulk of which is in the submucosa. At times, in the small intestine, it may protrude into the lumen and produce obstructive manifestations. This tumor is often multiple. Those examples of carcinoid that run a benign course cannot be differentiated on histological grounds from those which infiltrate and ultimately metastasize. A decision, therefore, as to whether or not a carcinoid is malignant, is based upon evidence of infiltration and metastases. Metastases may involve lymph nodes, not infrequently the liver and even on occasion, may be widespread. In the area immediately surrounding the tumor the intestinal musculature is frequently hypertrophied. Whether or not this is responsible for the intussusception which may occur on occasion is not clear.

In the appendix the tumors are small, rarely metastasize, and seldom produce symptoms. They are usually discovered as a coincidental finding. On occasion, however, the tumor itself may cause obstruction within the appendix and produce the picture of acute appendicitis. In the stomach benign carcinoids are a medical

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curiosity. Rarely has a malignant carcinoid of the stomach been seen and it produces symptoms usually as a result of local infiltration and metastases to the regional lymph nodes. It is estimated that from 80 to 95 per cent of all carcinoids are located in the region of the ileocecal valve, the most frequent site in the small intestine is the ileum. Involvement of the small intestine produces a syndrome consisting of recurrent and partial intestinal obstruction, intermittent diarrhea, pain and loss of weight. The diarrhea is often bloodless because of the submucosal growth of the carcinoid without any ulceration of the overlying mucosa. Those that arise in the small intestine are the ones that most frequently reveal malignant manifestations. About 25 to 50 per cent of carcinoid tumors

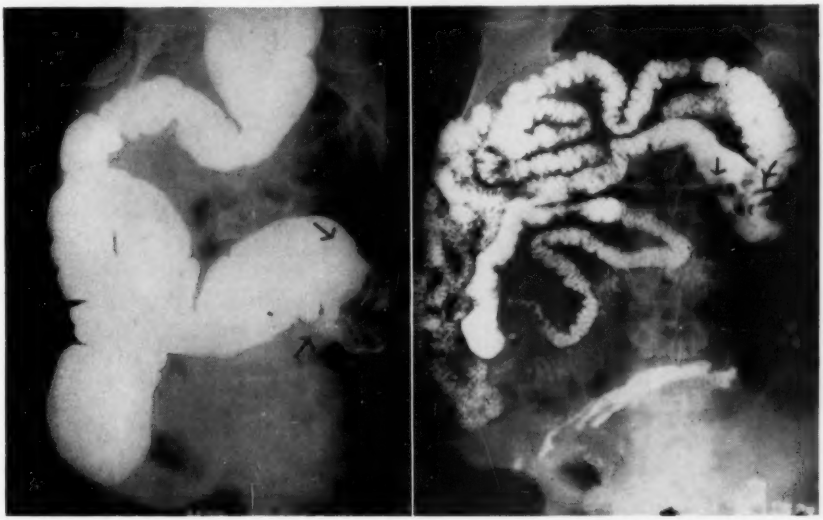

Fig. 1 Fig. 2

Fig. 1—X-ray picture of barium in colon showing areas of intussusception.
Fig. 2—X-ray picture of barium in small intestine showing defect from lesion in ileum.

of the ileum will eventually infiltrate or metastasize. A current concept is that all carcinoid tumor must be regarded as potentially malignant. Even those that infiltrate and metastasize, however, are compatible with relatively long periods of survival. Cases have been recorded of survival for over 15 years in the presence of liver metastases. When the rectum is involved the growth may be quite extensive and infiltrate submucosally and into the surrounding perirectal tissue. Behavior of the rectal carcinoid simulates very closely that of carcinoma of the rectum and it is usually indistinguishable on the clinical grounds. Biopsy of such a lesion may be mistaken for carcinoma or else may reveal no tumor cells because of the deep submucosal type of growth.

The following case reports and x-ray pictures illustrate some of the aspects of the behavior of these tumors.

Case 1:—A 50-year old male was admitted to the hospital with a history of acute abdominal pain of 24-hours' duration and absence of any bowel movements during that period of time. Examination revealed a distended abdomen that was tender in the right upper quadrant. X-ray picture of the barium enema showed an intussusception which measured 14 cm. (Fig. 1). Microscopic examination revealed the typical cellular pattern of carcinoid. No evidence of metastases was

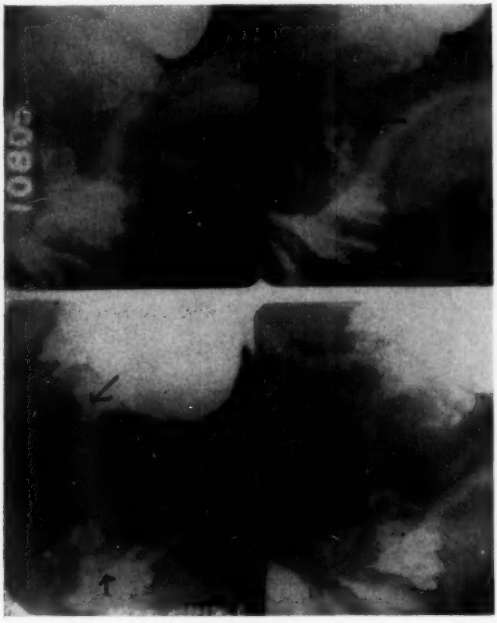

Fig. 3

Fig. 3—X-ray picture of barium in rectum showing narrowing of lumen due to infiltration of carcinoid tumor.

found in the abdominal exploration. The lymph nodes associated with the specimen did not reveal any evidence of tumor.

This case illustrates the acute type of onset with intestinal obstruction secondary to the intussusception. It also is an example of the less common form of involvement of the colon.

Case 2:—A 72-year old male with a history of intermittent abdominal cramps, bloody diarrhea and weight loss of several weeks duration. X-ray examination of the intestinal tract revealed a mass in the ileum (Fig. 2). Abdominal exploration

was performed and a segment of small intestine was resected. The mass was 4 cm. in diameter at its widest portion and infiltrated the mucosa and submucosa. There was no infiltration in the surrounding tissue and the regional lymph nodes were not involved. Histologic appearance was typical of carcinoid.

This case illustrates the typical manifestations that may occur with involvement of the small intestine. In this case bloody diarrhea was present because, as the specimen indicated there was ulceration through the mucosa.

Case 3:—A middle-aged male who was admitted with the chief complaint of constipation for 5 days, anorexia for two days and lower abdominal pains for two or three weeks. He had been entirely well until 2 months prior to admission. Four or five weeks prior to admission he noticed some bright red rectal bleeding. Rectal endoscopy revealed an area 8 cm. from the anus that was indurated and had polypoid protrusions (Fig. 3). At 17 cm. the sigmoidoscope was blocked. A biopsy was taken. Following this an anterior colon resection was performed. At the time of the resection nodules were found in the liver and there was enlargement of the regional lymph nodes. Histologic diagnosis of the specimen was carcinoid tumor, malignant. Several months later he was readmitted with abdominal distention, vomiting and a rapid downhill course and expired 4 months after the original operation. Postmortem examination revealed tumor nodules in the mesentery with a large mass of tumor 10 x 8 x 8 cm. adherent to the vertebrae. The liver weighed 3,400 gm. and its parenchyma was almost completely replaced by large white nodules. Metastatic carcinoid was also found in the regional nodes and pancreas, lungs and diaphragm. The heart had fibrosis and thickening of the tricuspid valve leaflets and of the right ventricular endocardium.

Case 3 illustrates the malignant behavior of the tumor and some of the early changes in the endocardium about which there have been numerous reports in recent years. Thorson, et al[1] has been credited with the first description of the syndrome of the association of malignant carcinoid with alterations in the heart valves. Millman in 1945[2], however, reported a case with a tricuspid valvular lesion and malignant carcinoid. He also described in excellent detail the various skin manifestations associated with this syndrome. At that time it was impossible for him to relate the two conditions specifically to each other because information was not available concerning 5-hydroxytryptamine. Following Thorson's report there have been innumerable descriptions of this syndrome. In the author's study[3] of 24 autopsy cases with carcinoid primary in the intestinal tract there were ten with metastases. There was a notable difference in the distribution of the cardiovascular lesions between those with and without metastases. Seven of the ten cases with metastases demonstrated endocardial fibrosis with involvement of the pulmonic and tricuspid valves. Only three of the 16 without metastases had any of these alterations. The endocardial changes varied in age, severity and extent. In some there was minimal fibrotic thickening which was diffuse or focal. In

others it was extensive and resulted in marked anatomic distortions of the valves. In some instances the valves exhibited an earlier and edematous type of involvement. In one case a fresh nonbacterial, thrombotic or verrucous type of endocarditis was superimposed upon a scarred valve. In a few instances there was fibrosis, at times extensive in the endocardium beneath the pulmonic valve ring. In one case mitral valve involvement was also present. The older and more advanced changes were found in those cases in which the carcinoid had metastasized. Advanced changes, however, were not necessarily limited to those with extensive hepatic metastases. Rambo, Gore and Vance[4] advanced the concept that the progressive and acquired changes in the valve may be related to some substances derived from the tumor tissue which exerts a deleterious effect on the endocardium. Discharge of the material into the right side of the heart, particularly derived from liver metastasis might account for the predominance of changes in this area. It is now definitely established that 5-hydroxytryptamine is elaborated at least in part from the enterochromaffin system and it has also been isolated in significant quantities from carcinoid tumors. It is also found in the urine of patients with metastatic carcinoid. This is used as a diagnostic test.

5-hydroxytryptamine has previously been known as seratonin or enteramine. This substance is believed to be responsible for the attacks of flushing and skin manifestations and the occasional asthmatic attacks that may occur in this syndrome. Attempts, however, to reproduce the endocardial lesions experimentally in rabbits with 5-hydroxytryptamine have so far failed to meet with success. The valvulitis may possibly be secondary to alteration in circulatory mechanism rather than to direct metabolic action.

The isolation of 5-hydroxytryptamine proved that enteramine and serotonin were the same substance. This substance had two names for many years because the investigation that led to the isolation of 5-hydroxytryptamine was carried out independently by two groups. Erspamer and his group[5] began by attempting to isolate the substance that imparts of the peculiar histochemical properties to the enteramine. Rapport and his group[6] were interested in isolating the factor that produced vasoconstriction in serum and defibrinated blood. This group extracted a substance from purified preparations of beef serum and named it serotonin. 5-hydroxytryptamine is now regarded as the substance responsible for the syndrome associated with carcinoid tumors. It has a widespread and varied pharmacologic action. Study is difficult because of its variability in action in different species. In general it is believed that it is elaborated by the enterchrome cells located mainly in the gastrointestinal tract, carried by the platelets, released from these platelets on their disintegration and neutralized to a great extent in the liver and lungs. Significant concentrations of the substance are found in the central nervous system. It liberates adrenalin on injection into the mesenteric artery of the cat, and is the vasoconstrictive factor of blood platelets. Of tremendous interest and currently the subject of numerous investigations is the fact that it is antagonized by lysergic acid diethylamide. The latter is the

substance which has induced a schizophrenic-like state experimentally in human volunteers. Some observers believe that it is intimately concerned with the maintenance of normal mental processes[7]. It is generally regarded as a stimulant of smooth muscle. The precursor of 5-hydroxytryptamine is tryptophan. Tryptophan is one of the deficient elements in the diet of the South African Bantu who develop endomyocardial fibrosis. This is believed to be a nutritional deficiency disorder. Perhaps overproduction of 5-hydroxytryptamine partially depletes the tryptophan reserves of the body and in this way may contribute to the development of the subendocardial fibrosis that involves the valves. Although the real physiological role of 5-hydroxytryptamine in the human has not as yet been established, its isolation has opened vast areas for investigation.

Summary

1. Benign carcinoid tumors may produce a variety of manifestations as a result of local involvement of the intestinal tract, e.g. obstruction, intussusception, diarrhea, hemorrhage, pain and weight loss.

2. Carcinoid tumors are frequently malignant but long survival in the presence of metastases is not uncommon.

3. The syndrome associated with malignant carcinoid consists of predominantly right-sided valvular endocardial fibrosis, a peculiar type of skin telangiectasia, skin cyanosis and blushing secondary to vasomotor changes and asthmatic-like symptoms due to bronchoconstriction.

4. The substance responsible for this syndrome is believed to be 5-hydroxytryptamine, regarded as a specific hormone of the enterchromaffin cell system and also elaborated in great quantities by carcinoid tumors.

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Discussion

Dr. I. Snapper (Brooklyn, N.Y.):—The very interesting facts Dr. Spain has reported shed a completely new light on certain chapters of pathology.

These carcinoids which usually take issue from the intestinal canal produce a substance, hydroxytryptamine, which causes vasomotor reactions as mottling of the skin, together with changes of the collagen of the heart valves, especially of the right heart.

If we remember that Raynaud's syndrome and collagen changes are very frequent in *lupus erythematosus*, then it seems possible that in the future we might be able to define the chemical substances which cause the syndrome of *lupus erythematosus*.

Thus carcinoids, which until now were mainly of interest to the pathologist, all at once assume physiopathologic significance. The new findings open new fields and may lead to better understanding of chemical compounds which play a role in the etiology of certain diseases, especially of the mysterious diseases of the collagen.

Dr. Owen H. Wangensteen (Minneapolis, Minn.):—The problem of carcinoid is certainly an area in which we are putting together items or components of a picture puzzle which are beginning to make an indelible impression upon our understanding.

I can recall reading the paper of Thorsen of June, 1954, in the American Heart Journal [*47*:795 (June) 1954]. He, representing a group from one of the hospitals in Sweden, reported upon seven such cases of carcinoid with right heart failure.

I had long years previously operated upon a fellow by the name of George Simons in the middle 30's, just making an enteroanastomosis, because George had bowel obstruction and metastases in the liver. At the time, I thought he had an adenocarcinoma of the ileum.

Years went by, and I realized we had made an error in diagnosis; that the lesion undoubtedly was a carcinoid. After about seven years, George became re-obstructed so I re-operated upon him; I took out the tumor as well as the enteroanastomosis. The suspicioned diagnosis of carcinoid was confirmed. Several of the large metastatic nodules in the liver also were excised, one of which weighed 220 grams.

When I read the Thorsen paper in early 1955, I sought to get in touch with George. He had then survived for more than 16 years. He had just died and had been buried; the cause of death was heart disease at age 80 years. The syndrome of right-sided heart failure and cyanosis which frequently attends carcinoid of

the ileum when it has metastasized to the liver, makes these tumors of great interest to the surgeon.

Did my patient with metastasis to the liver, who survived for more than 16 years have a cancer? It is a good question. Ordinarily, one thinks of a tumor with metastasis as being malignant. Perhaps, in the end, my patient died because of physiologic effects of serotonin intoxication from the carcinoid described by Dr. Spain.

I was very much intrigued by one remark Dr. Spain made. These cells are delimited wholly to the alimentary tract. As Dr. Brody, of the Pharmacology Section at the N.I.H. at Washington, and his co-workers have shown, this drug does affect the blood pressure. Would one be justified in trying to do selective resections in the alimentary tract for hypertension? I don't know. There have been thousands of operations on the sympathetic nervous system—many of them useless. Certainly, one could get along very well after excision of 90-100 cm. of ileum. Perhaps this experiment should be tried for hypertension. Probably it would be more proper to determine whether any patients with hypertension have had excision of a goodly segment of the terminal ileum and right colon—and whether such a procedure had a beneficial effect upon the blood pressure. If one could know from the work of Masson or others where the richest distribution of the argentaffine cells in the intestine are, such information might prove useful.

I am put in mind of a Norwegian upon whom I operated long years ago who had two diseases, exophthalmic goiter and peptic ulcer. One week I took him down to the amphitheatre clinic after having operated upon his thyroid a few days previously. I just became ears instead of a voice in speaking to the students. My patient took over the clinic, got up from the wheel chair and gave the students a discourse on the accomplishments of the University Hospital and its Staff. Three weeks after the thyroidectomy, I took him down to the amphitheatre clinic again, after having done a three-quarter resection of the stomach for the peptic ulcer. This time the patient had nothing to say. He was completely subdued and was at peace with himself and the world. It is possible that selective excision of certain parts of the alimentary tract might not be a bad experimental venture for hypertension.

I realize I am talking, really, with my tongue in my cheek about all this. Dr. Snapper has effected the role of a prophet. The Bible warns us about the testimony of prophets, and I hesitate to affect even the role of a minor prophet—could this be a prophecy that might come true?

EVALUATION OF A NEW ATROPINE-BRAND ANTICHOLINERGIC*

Clinical, Gastric Secretory and Roentgenological Effects in Peptic Ulcer and Gastrointestinal Functional Disorders

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The literature abounds with recommended treatments for peptic ulcer. Atropine has always been the most widely used anticholinergic in the treatment of this disease. With the introduction of methantheline and subsequently other quaternary ammonium compounds, the era of synthetic anticholinergics with their many promising favorable effects had arrived. The test of time has shown that much is desired before these drugs can replace atropine with its conceded limitations and side-effects.

It is noteworthy that in recognition of the limitations of the quaternary ammonium compounds there is a tendency to resume treatment with atropine-brand medications. This presentation concerns itself with a clinical, roentgenological and gastric analyses evaluation of varying doses of an atropine-brand anticholinergic, Tropinox®, and also a combination of this preparation with chemical antacids, Duocotin®. The drug, an aminoxytropine tropate hydrochloride, is an atropine aminoxide hydrochloride.

Laboratory animal experimentation with atropine aminoxide hydrochloride[1] revealed that "a. Large doses can be tolerated for prolonged periods without evidence of cumulative toxicity. b. It is less toxic and has less pronounced effect on blood pressure than methantheline, atropine or homatropine methyl bromide. c. It possesses a high index of anticholinergic activity. d. It is equal with methantheline as an inhibitor of stomach contractions and that it is effective in relaxing ileal contractions. e. It is more effective than methantheline in blocking the vasopressor effects of electrical stimulation of the vagus nerve. f. In 1 to 2 mg. doses it is equally effective in preventing histamine induced gastric secretion as 50 mg. of methantheline under similar conditions."

Clinical Material

This investigation included 29 patients that were clinically and roentgenologically studied to establish their diagnoses. Seven patients were diagnosed as having gastrointestinal *functional* disorders; one had an associated biliary

*The atropine-brand preparation was made available through a grant by The Harrower Laboratory, Inc. now a part of Warner-Chilcott Laboratories, New York, N. Y. and is manufactured under the trade-name Tropinox®. Appreciation is hereby expressed for the grant.

†Assistant Clinical Professor of Medicine, New York Medical College; Consultant Gastroenterologist, Queens General Hospital Medical Center, Jamaica, N. Y.

tract dyskinesia, another diverticulosis of the descending colon and a third had a noncomplicated transitory hiatus hernia. These seven patients (Cases 1-7) will be referred to as Group A, of which Cases 1-4 and 5-7 will respectively be referred to as Group A*x* and Group A*y*. The purposes of these subdivisions are explained under "Procedures". Note that Group A*x* had 4 patients while Group A*y* had 3 patients. Cases 8-14 will be referred to as Group B and its subdivisions of Cases 8-11 and 12-14 will be known as Groups B*x* and B*y* respectively. The reasons for these subdivisions are likewise explained under "Procedures". Note that Group B*x* had 4 patients and B*y* had 3 patients. Group B includes 5 patients with chronic duodenal cap peptic ulcers, 1 with a transitory hiatus hernia that had had a previous episode of hematemesis and an associated duodenitis, and 1 subtotally gastrectomized patient with two subsequent episodes of hematemesis due to a stomal ulcer that was visualized on gastroscopy. This last patient had no free hydrochloric acid on gastric analysis subsequent to histamine stimulation. The remaining 15 patients had chronic duodenal cap peptic ulcers and were subdivided into 3 groups of 5 patients. They will be referred to as Group S, Group T, and Group M.

The sex and age incidences were as follows:

Group A (Cases 1-7)—5 males ages 32, 42, 49, 54 and 72 years and 2 females ages 30 and 54 years.

Group B (Cases 8-14)—5 males ages 31, 35, 38, 44 and 59 years and 2 females ages 42 and 59 years.

Group S (Cases 15-19)—4 males ages 35, 42, 45 and 55 years and 1 female age 56 years.

Group T (Cases 20-24)—4 males ages 33, 37, 38 and 64 years and 1 female age 40 years.

Group M (Cases 25-29)—3 males ages 41, 67 and 74 years and 2 females ages 39 and 60 years.

Procedures

A standardized history and physical examination was carried out on each patient prior and subsequent to the investigation. Fluoroscopy and roentgenography of the intestinal tract, using the usual preparations and conventional methods, was likewise a standard procedure before and after administration of Tropinox, the medicament under study. All of the patients were ambulatory, on the same bland diet and used supplementary vitamins in the form of 1 tablet of Enforbec during breakfast and dinner.

The second clinical and roentgenological surveys were conducted after the patients had used the medicament for a specified time with doses varying in each Group as follows:

TABLE I

Sex	Age Years	Case	Clinical and X-ray Diagnosis	Imroved		Pylorospasms	
				Clinically	X-ray	Before T	After T
M	42	1	No organic G-I lesion G-I neurosis	N	Y	Y	Y
M	32	2	G-I neurosis Irritable colon	Y	N	Y	Y
F	30	3	G-I neurosis Biliary tract dyskinesia	Y	N	N	Y
M	54	4	No organic G-I lesion	N	N	Y	Y
M	44	8	Chronic duodenal cap peptic ulcer	Y	Y	Y	Y
F	59	9	Chronic duodenal cap peptic ulcer symptom-complex (Hematemesis 2 mo. ago)	Y	Y	Y	Y
M	31	10	Chronic duodenal cap peptic ulcer	Y	Y	Y	Y
M	35	11	Stomal ulcer (2 hematemesis episodes) in a subtotally gastrectomized case	Y	Y	(Subtotally gastrectomized)	
M	49	5	G-I neurosis. Some descending colon diverticulosis	N	Y	Y	Y
M	72	6	G-I neurosis	Y	Y	Y	N
F	54	7	Transitory hiatus hernia without complications	N	N	N	N
M	59	12	Chronic duodenal cap peptic ulcer	Y	Y	N	N
M	38	13	Transitory hiatus hernia with one episode of hematemesis. Assoc. duodenitis.	Y	N	Y	Y
F	42	14	Chronic duodenal cap peptic ulcer	Y	Y	Y	N

TABLE I (*continued*)

Sex	Age Years	Case	Clinical and X-ray Diagnosis	Improved		Pylorospasms	
				Clinically	X-ray	Before T	After T
M	42	15	Chronic duodenal cap ulcer	Y	Y	Y	Y
M	55	16	Chronic duodenal cap ulcer	Y	Y	Y	N
F	56	17	Chronic duodenal cap ulcer	Y	N	Y	Y
M	45	18	Chronic duodenal cap ulcer	Y	Y	Y	N
M	35	19	Chronic duodenal cap ulcer	N	N	Y	N

The above, Group S, was treated with 0.5 mg. Tropinox 1 hr. p.c. and 1 mg. Tropinox before retiring.

M	38	20	Chronic duodenal cap ulcer	Y	Y	Y	N
F	40	21	Chronic duodenal cap ulcer	Y	Y	Y	Y
M	33	22	Chronic duodenal cap ulcer	Y	Y	Y	Y
M	37	23	Chronic duodenal cap ulcer	Y	Y	Y	Y
M	64	24	Chronic duodenal cap ulcer	N	N	Y	Y

The above, Group T, was treated with 1 mg. Tropinox ½ hour after breakfast and before retiring.

F	39	25	Chronic duodenal cap ulcer	Y	Y	Y	Y
F	60	26	Chronic duodenal cap ulcer	Y	Y	Y	N
M	67	27	Chronic duodenal cap ulcer	N	N	Y	Y
M	41	28	Chronic duodenal cap ulcer	Y	Y	Y	Y
M	74	29	Chronic duodenal cap ulcer	Y	N	Y	Y

The above, Group M, was treated with 2 tablets Duocotin 2 hr. p.c. and before retiring.

The heavier dark line separates the patients as to dose of drug used; those above received 1 mg. while those below 0.75 mg. The patients with organic lesions were found to improve more clinically and to develop more favorable x-ray evidence of improvement at the completion of the 10-day investigation period than those having functional disorders. Groups S, T and M developed favorable clinical and x-ray improvements.

Key: N = No appreciable improvement. Under Pylorospasms N = None
Y = Varying degrees of improvement and varying degrees of pylorospasms.

TABLE II

Group	Case	H-P		OAP		H-B		NAU		BEL		EFP		VOM		E-B		POM		E-F		CON		DIA.	
		B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
A*x*	1	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	Y	N	N	N	Y	Y	Y	Y	N	N
A*x*	2	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	N	N	Y	N	Y	Y	N	N	Y	N
A*x*	3	N	N	N	N	Y	N	N	N	Y	Y	N	N	N	N	N	N	N	N	Y	N	Y	N	N	N
A*x*	4	N	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	Y	N	N	N	N	N	Y	N	N
B*x*	8	Y	N	N	N	N	N	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	N	N	Y	N	N	N	N
B*x*	9	N	N	Y	N	N	N	N	N	Y	Y	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	N	N
B*x*	10	N	N	Y	N	N	N	N	N	Y	N	Y	N	N	N	Y	N	N	N	Y	N	N	Y	N	N
B*x*	11	Y	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
A*y*	5	N	N	Y	Y	N	N	N	Y	N	N	Y	Y	N	N	Y	Y	N	N	Y	Y	N	N	N	N
A*y*	6	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N
A*y*	7	N	N	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	N	Y	N	N	N	Y	Y	Y	N	N
B*y*	12	Y	N	N	N	Y	N	Y	N	N	N	Y	Y	Y	N	N	N	Y	N	N	N	N	N	N	N
B*y*	13	N	N	Y	Y	Y	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	Y	Y	N	N
B*y*	14	Y	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	Y	N	Y	N	N	N

TABLE II (*continued*)

Group	Case	H-P		OAP		H-B		NAU		BEL		EFP		VOM		E-B		POM		E-F		CON		DIA.	
		B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
S	15	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	N	N	N	N	N	N	Y	Y	N	N
S	16	Y	N	Y	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N
S	17	N	N	Y	Y	N	Y	N	N	Y	Y	Y	N	N	N	N	N	N	N	N	Y	Y	N	N	N
S	18	Y	N	N	N	Y	N	N	N	Y	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N
S	19	Y	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	N	Y	Y	N	N	Y	N
T	20	Y	N	N	N	Y	N	Y	N	Y	N	Y	N	N	N	Y	N	N	N	Y	N	Y	N	N	N
T	21	Y	N	N	N	Y	N	N	N	Y	Y	Y	N	N	N	Y	N	N	N	N	N	N	N	N	N
T	22	Y	Y	Y	Y	N	N	Y	N	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N
T	23	Y	N	Y	N	Y	N	Y	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	Y	N	N
T	24	Y	N	N	N	Y	Y	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	N	N
M	25	Y	N	Y	N	N	N	Y	N	Y	Y	Y	Y	N	N	N	N	N	N	Y	Y	Y	N	N	N
M	26	Y	N	Y	N	N	N	N	N	Y	N	Y	N	N	N	N	N	N	N	Y	Y	Y	N	N	N
M	27	Y	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	N	N	N	N	N	N	Y	N	Y	N	N	N
M	28	N	N	Y	N	N	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	N	Y	Y	N	N
M	29	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	Y	N	Y	N	N	N	N	Y	Y	Y	N	N

The variation in the doses used appeared to have no appreciable differences of the symptomatic effects. The symptoms of the patients with organic lesions were more favorably influenced than those having functional disorders.

Key:

H-P = Hunger-pain
OAP = Other abdominal pain
H-B = Heart-burn
NAU = Nausea
BEL = Belching
EFP = Epigastric fulness and pressure
VOM = Vomiting
E-B = Epigastric-burning
POM = Passage of mucus
E-F = Excessive flatus
CON = Constipation
DIA = Diarrhea
B = Before treatment
A = After the treatment
N = No
Y = Yes

Groups A*x* and B*x*—1 mg. of Tropinox 1 hour after breakfast, lunch and dinner and before retiring for 10 days.

Groups A*y* and B*y*—0.75 mg. of Tropinox 1 hour after breakfast, lunch and dinner and before retiring for 10 days.

Group S—0.5 mg. of Tropinox 1 hour after breakfast, lunch and dinner and 1 mg. before retiring for 4 weeks.

Group T—1 mg. of Tropinox ½ hour after breakfast and before retiring for 4 weeks.

Group M—0.5 mg. of Tropinox (in the form of Duocotin*) 2 hours after breakfast, lunch and dinner and before retiring for 4 weeks.

It was deemed adequate to use a 10-day survey period for Groups A and B because the total daily dose of Tropinox used by each member patient was greater than that of each member patient of the other Groups. The 24-hour x-ray observations were discontinued at the completion of the surveys of Groups A and B because they were noncontributory to this investigation.

It was recognized that the Tropinox should have both clinical and x-ray influence on the gastrointestinal tract during the course of treatment. The "immediate" effect on gastrointestinal activity, however, would not be brought into view if the drug would not be used during the posttreatment x-ray investigation. Hence, the second x-ray series were conducted 4 hours after the patients had ingested the medicament in the following doses: Group A*x* and B*x*—1 mg.; Group A*y* and B*y*—0.75 mg.; Group S—0.5 mg.; Group T—1 mg.; Group M—0.5 mg. in the form of Duocotin. The doses were repeated every 6 hours throughout these x-ray investigations.

Fractional gastric analyses were carried out under histamine stimulation before and after the specified periods of treatment with the Tropinox.

The initial gastric analyses were conducted using the following methods: a. The patients reported on the morning of study without having eaten or drunk anything. b. A lubricated Levin tube was introduced into the stomach intranasally and the fasting gastric residue completely withdrawn and part was set aside as the first specimen. c. The stomach was lavaged through the Levin tube using 200 c.c. of distilled water and the washings discarded. d. The patient was then given a subcutaneous injection of histamine phosphate 1-1000 (0.045 mg.). e. Subsequently some of the gastric secretion was withdrawn at 15 minute intervals over a 90-minute period and specimens set aside. f. Each

*Each Duocotin tablet contains 0.25 mg. of Tropinox, 100 mg. each of aluminum hydroxide dried gel and magnesium trisilicate, 90 mg. of calcium carbonate, 84 mg. of magnesium oxide and Vitamins A and D, ascorbic acid, thiamine mononitrate, riboflavin, niacinamide, calcium pantothenate, pyridoxine hydrochloride, Vitamin B_{12} and folic acid all in the average accepted doses.

TABLE II-A

Group	Ax plus Bx (1 mg. q.i.d.)		Ay plus By (0.75 mg. q.i.d.)		S (0.5 mg. t.i.d. plus 1 mg. before retiring)		T (1 mg. b.i.d.)		M (0.5 mg. q.i.d. in the form of Duocotin)	
Symptoms	Before	After	Before	After	Before	After	Before	After	Before	After
Hunger-pain	2	0	2	0	4	1	5	1	4	2
Other abd. pain	3	1	2	2	4	1	2	1	5	1
Heart-burn	3	3	3	1	3	2	4	1	1	1
Nausea	2	0	0	1	1	0	3	2	2	0
Belching	7	5	3	2	4	2	3	2	3	3
Epigast. fulness and pressure	2	3	4	3	5	2	5	1	5	3
Vomiting	1	0	0	0	1	0	0	0	1	0
Epigast. burning	3	1	2	2	0	0	2	0	2	0
Passing of mucus	2	1	1	0	0	0	0	1	0	0
Excessive flatus	6	3	3	2	1	2	2	0	3	3
Constipation	3	5	3	3	2	1	1	2	5	3
Diarrhea	1	0	0	0	1	0	0	0	0	0

Summary of the symptomatic effects with treatment of varying doses of Tropinox. The above figures refer to the number of patients.

of these 7 specimens was filtered through 4 layers of gauze. g. An analysis of free hydrochloric acid and total acidity was carried out in the usual manner using Toepfer's reagent and phenolphthalein as indicators and N/10 sodium hydroxide for titration. The results were expressed in the terms of clinical units.

The second gastric analyses were conducted on the morning following the last day of treatment with Tropinox. Therefore, the last dose was taken before retiring on the previous evening. This should be considered in evaluating the gastric residue specimen against the initial gastric residue specmen. The methods for gastric analyses were the same as outlined above with one exception. Following the gastric lavages as mentioned above in step c. a 15 c.c. solution of distilled water in which Tropinox had been dissolved was introduced into the stomach through the Levin tube. The amount of Tropinox dissolved for each case was the same as the dose used by the various groups 4 hours prior to starting their posttreatment x-ray study. Another 10 c.c. of distilled water was introduced through the Levin tube for purposes of washing into the stomach any part of the aforementioned solution that might have remained in the tube. Fifteen minutes were allowed for absorption of the Tropinox before the histamine phosphate injection was given as in step d. The time determinations for the free hydrochloric acid and total acidity in the various specimens are in relation to the histamine phosphate injections and not to the administration of the Tropinox solution.

The findings on the second gastric analyses of Group M bear special consideration in evaluating the comparative results because Duocotin has component parts that are alkaline and therefore are antacids.

Observations

It is appreciated that the recorded clinical observations are influenced by many factors. The "over-all" clinical impressions are based on symptomatic relief. It is acknowledged that clinical evaluations based on patients' impressions, such as subjective symptoms, are at best not too reliable. Limited as we are by having to accept patients' subjective impressions, however, the general impression gained was that there was clinical improvement regardless of the daily dose of the medicament under investigation.

Symptomatology:—It is interesting to note in Table II that very little appreciable symptomatic changes developed in Group A, regardless of the Tropinox dose that was used. One less patient of Group A*y* and one more of A*x* complained of belching after the 10-day period of medication; two of A*x* developed epigastric fulness and pressure; one more of A*y* experienced epigastric burning; one each of A*x* was relieved of passing mucus with the feces, of passing excessive flatus per rectum and of diarrhea. The *number* of patients in Group A free of or experiencing other symptoms was not altered. Case 3 was relieved of her constipation.

TABLE III

Group	Case	Dryness of Mouth	Blurring of Vision	Constipation	Difficulty on Starting Urinary Stream	Feeling of Well-Being	Miscellaneous Untoward Effects
Ax	1	Y	Y	Y	N	N	N
Ax	2	N	N	N	N	Y	N
Ax	3	Y	N	N	N	Y	N
Ax	4	Y	Y	Y	Y	Y	N
Bx	8	N	Y	N	Y	Y	N
Bx	9	Y	N	N	N	Y	N
Bx	10	Y	Y	Y	Y	N	N
Bx	11	Y	Y	Y	N	Y	N
Ay	5	Y	N	N	N	N	N
Ay	6	Y	N	N	Y	Y	N
Ay	7	Y	N	Y	N	N	N
By	12	N	N	Y	N	N	N
By	13	N	N	N	N	N	N
By	14	Y	Y	N	N	Y	N
S	15	N	N	Y	N	Y	N
S	16	N	N	N	N	Y	N
S	17	Y	Y	N	N	N	N
S	18	N	N	N	Y	N	N
S	19	Y	N	N	N	Y	N
T	20	N	N	N	N	N	N
T	21	N	N	N	N	N	N
T	22	N	Y	N	N	Y	N
T	23	Y	N	Y	N	N	N
T	24	Y	Y	Y	N	N	generally "unhappy" Y
M	25	Y	Y	Y	N	Y	N
M	26	Y	N	N	N	N	N
M	27	Y	N	N	N	N	N
M	28	Y	N	Y	N	N	N
M	29	Y	N	Y	N	N	N

The side-effects were of greater intensity and more frequent when the large dose of the medication was used. With the exception of xerostomia, side-effects were more frequent in those patients having organic lesions. None of the side-effects were severe.

Key: N = None
Y = Yes

Group B comprised, as previously mentioned of organically ill patients, does present favorable responses to Tropinox without significant variations as to dosage of this medicament used in this investigation. All patients were relieved of their hunger-pain and the two patients of B*x* experiencing other vague abdominal pain were relieved. The two patients of B*y* experiencing heart-burn were relieved. The nauseated B*x* case was relieved and three other B*x* cases no longer complained of belching. Vomiting ceased in the B*x* case that previously experienced same. None of Group B had epigastric burning after treatment. Two cases of B*x* were relieved of passing excessive flatus per rectum. One B*y* patient (Case 14) was relieved of passing mucus and excessive flatus per rectum and her constipation.

Hunger-pain was reduced most by the large dose of the medication and was reduced least when used in the form of Duocotin. There is a strong probability that this was due to the fact that Group M included the more severely sick patients. Group M did, however, present evidence that their symptoms became less intense and the effect of the drug continued for a longer period of time than that developed in the other Groups.

The over-all clinical improvements closely approximated each other by the various Groups except Group A, the gastrointestinal functional disorder patients. The other Groups developed clinical improvements of about 80 per cent or more, while Group A presented only about 43 per cent.

Side-effects:—It is noteworthy that Group B had a greater number of side-effects than Group A. This seems to further indicate that of the patients studied those with organic lesions were effected more by the Tropinox than those having functional gastrointestinal disorders. The side-effects of those receiving the larger dose of the medicament were of greater intensity and developed in more patients. In most instances, however, the intensity was minimal. All side-effects immediately ceased after the medicament was stopped.

Xerostomia developed in 85 per cent of Group A and 57 per cent of Group B and was the only side-effect that occurred more frequently in Group A. This symptom developed in 75 per cent of A*x* plus B*x* and in 66 per cent of A*y* plus B*y*. Mydriasis occurred in 62 per cent of those patients receiving the larger dose (1 mg.) of Tropinox and in 16 per cent of those receiving the small dose (0.75 mg.).

Interference with starting the urinary stream developed in 37 per cent of A*x* plus B*x* and 16 per cent of A*y* plus B*y* groups. Euphoria was experienced by 62 per cent of A*x* plus B*x* and 33 per cent of A*y* plus B*y*.

Constipation developed in 4 patients and increased or continued in 4 other patients. Two patients were relieved of their constipation. This symptom was experienced by 62 per cent of A*x* plus B*x* and 50 per cent of those receiving the small dose of Tropinox.

TABLE III-A

SIDE-EFFECTS OF VARYING DOSES OF TROPINOX

Side-effects	Group Ax + Bx (1 mg. q.i.d.) (8 patients)	Group Ay + By (0.75 mg. q.i.d.) (6 patients)	Group S (0.5 mg. t.i.d. + 1 mg.) (5 patients)	Group T (1 mg. b.i.d.) (5 patients)	Group M (0.5 mg. q.i.d. in form of Duocotin) (5 patients)
Xerostomia	6 (75%)	4 (66.6%)	2 (40%)	2 (40%)	5 (100%)
Mydriasis	5 (62.5%)	1 (16.6%)	1 (20%)	2 (40%)	1 (20%)
Constipation	5 (62.5%)	3 (50%)	1 (20%)	2 (40%)	3 [5 patients (60%) were constip. before study]
Difficulty on starting urinary stream	3 (37.5%)	1 (16.6%)	1 (20%)	0 (—%)	0 (—%)
Euphoria	5 (62.5%)	2 (33.3%)	3 (60%)	1 (20%)	1 (20%)
Miscellaneous	0 (—%)	0 (—%)	0 (—%)	generally "unhappy" 1 (20%)	0 (—%)

TABLE IV

Group	Case	Gastric Residue at 3 hours		Head of Barium Column at 3 hours		Tail of Barium Column at 3 hours	
		Before T	After T	Before T	After T	Before T	After T
Ax	1	N	N	Mid descend. colon	Cecum	Prox. ileal coils	Distal ileal coils
Ax	2	N	Y	Distal descend. colon	Distal ileal coils	Terminal ileal coils	Stomach
Ax	3	N	Y	Cecum	Distal ileal coils	Proximal jejunum	Stomach
Ax	4	Y	Y	Mid ascend. colon	Mid ileal coils	Stomach	Stomach
Bx	8	N	N	Ileocecal juncture	Cecum	Mid ileum	Proximal ileal coils
Bx	9	N	Y	Mid trans. colon	Mid ileal coils	Distal jejunal coils	Stomach
Bx	10	N	Y	Hepatic flex.	Dist. ileal coils	Prox. jejunum	Stomach
Bx	11	Y	N	Distal ileal coils	Hepatic flex.	Stomach	Terminal ileum
Ay	5	N	N	Distal ileal coils	Cecum	Dist. jejunal coils	Duodenal cap
	6	Y	N	Descend. colon	Mid ileal coils	Stomach	Duodenal cap
Ay	7	N	N	Mid ascend. colon	Cecum	Prox. ileal coils	Duodenal cap
By	12	N	N	Rectum	Rectum	Mid ileal coils	Prox. ileal coils
By	13	N	Y	Dist. ileal coils	Dist. ileal coils	Prox. jejunal coils	Stomach
By	14	Y	N	Hepatic flexure	Mid ileal coils	Duodenum	Dist. jejunal coils

TABLE IV (*continued*)

Group	Case	Gastric Residue at 3 hours		Head of Barium Column at 3 hours		Tail of Barium Column at 3 hours	
		Before T	After T	Before T	After T	Before T	After T
S	15	N	N	Distal ileal coils	Terminal ileal coils	Distal jej. coils	Prox. ileal coils
S	16	N	N	Hepatic flexure	Mid ileal coils	Mid ileal coils	Dist. jejunal coils
S	17	Y	N	Dist. ileal coils	Terminal ileal coils	Stomach	Dist. jejunal coils
S	18	Y	N	Dist. ileal coils	Mid ascend. colon	Stomach	Dist. ileal coils
S	19	N	N	Splenic flex.	Mid ileal coils	Mid ileal coils	Mid ileal coils
T	20	N	Y	Dist. trans. colon	Dist. ileal coils	Dist. ileal coils	Stomach
T	21	N	Y	Mid ascend. colon	Mid ileal	Mid jejunal coils	Stomach
T	22	N	Y	Mid trans. colon	Mid trans. colon	Prox. ileal coils	Stomach
T	23	N	Y	Cecum	Mid ascend. colon	Prox. ileal coils	Stomach
T	24	N	Y	Terminal ileal coils	Prox. ileal coils	Dist. jejunal coils	Stomach
		Before Duocotin	After Duocotin	Before Duocotin	After Duocotin	Before Duocotin	After Duocotin
M	25	N	Y	Mid trans. colon	Dist. ileal coils	2nd portion of duodenum	Stomach
M	26	Y	N	Terminal ileal coils	Dist. ileal coils	Stomach	Prox. ileal coils
M	27	Y	Y	Dist. ileal coils	Terminal ileal coils	Stomach	Stomach
M	28	N	N	Dist. trans. colon	Mid ascend. colon	Terminal ileal coils	Prox. ileal coils
M	29	N	N	Mid descend. colon	Terminal ileal coils	Dist. ileal coils	Mid ileal coils

At the 3rd hour of x-ray studies the incidence of gastric residue was increased when the 1 mg. of Tropinox was used. The amount of the drug used in these studies did not seem to influence the resultant decrease of intestinal motility to an appreciable greater extent in those patients with ulcers than those experiencing functional disorders.

Key: N = None
Y = Varying amounts of gastric residue
BT = Before using Tropinox
AT = After the 10-day trial period with the medicament.

The dose of Tropinox having been reduced for Groups S, T and M, the resultant side-effects became generally less. Euphoria was present in 60 per cent of Group S and xerostomia affected 100 per cent of Group M. This latter Group consisted of 5 patients (100 per cent) having constipation with only 60 per cent similarly afflicted during treatment.

Roentgenology:—The procedure for x-ray study was previously discussed. In the absence of actual organic pyloric obstruction, a five-minute or more delay in the starting of the passage of the contrast barium meal into the duodenum was considered as due to pylorospasms. Seventy-five per cent of each of the Groups A*x* and B*x* had pylorospasms before the Tropinox study was started. One hundred per cent of Group A*x* and 75 per cent of B*x* had pylorospasms during the final x-ray studies. Groups A*y* and B*y* each presented pylorospasms in 66 per cent and 33 per cent of cases respectively at the first and second x-ray examinations.

All of the patients of Groups S, T and M had pylorospasms prior to using Tropinox. The posttreatment x-ray studies revealed pylorospasms in 40 per cent of Group S and 80 per cent of Group T and also Group M.

The pretreatment x-ray surveys of Groups A and B revealed a 25 per cent gastric residue at the 3-hour period. Their posttreatment studies revealed some gastric residue in 75 per cent of Group A*x*, 50 per cent in B*x*, none in A*y* and 25 per cent in B*y*. The increase in Groups A*x* and B*x* may be due to the dose of Tropinox used by these patients. It is apparent that the smaller dose, 0.75 mg., of the medicament had little influence on the 3-hour gastric residue in patients A*y* and B*y*.

The 3-hour x-ray studies of Groups S, T and M revealed respectively a 40 per cent, none and 40 per cent pretreatment and none, 100 per cent and 40 per cent posttreatment gastric residue. These percentages pertain to the number of patients and not to the amount of gastric residue.

There was no gastric residue in any of the 6-hour pretreatment x-ray studies. Two patients of Group B*x* and 1 patient of Group T had some gastric residue at their 6-hour posttreatment x-ray surveys. These 3 patients had chronic duodenal cap ulcers. None of the patients studied at 24 hours revealed the presence of any gastric residue.

Evaluation of the positions of the head and tail of the barium column at the 3-, 6- and 24-hour periods revealed a decrease in intestinal motility in the posttreatment x-ray studies of Groups A and B. The 25 per cent smaller dose of Tropinox used by Groups A*y* and B*y* had practically the same decreasing effect on intestinal motility as did the 1 mg. dose. In the posttreatment x-ray studies Groups B*x* and B*y* presented less decrease in intestinal motility than did the patients having functional disorders (Groups A*x* and A*y*).

In evaluating the influence of the medicament under study on intestinal motility in Groups S, T and M one must give recognition to the dose of the drug taken 4 hours prior to the x-ray investigations and every 6 hours thereafter. Group S had taken 0.5 mg., Group T had taken 1 mg. and Group M had taken 0.5 mg. in the form of Duocotin. There was practically no x-ray evidence of decreased intestinal motility in Group S at the 3rd and 6th hour periods; considerable decrease in Group T; moderate decrease in Group M.

Favorable clinical response to a medicament is usually observed before evidence of healing is noted on x-ray study. X-ray improvement in Group A (functional disorders) was based on the posttreatment fluoroscopic evidence of reduction in the time and/or intensity of pylorospasms and irritability of the gastrointestinal tract. Improvement in Group B was evidenced by the lesions appearing smaller and/or being no longer visualized and by reduction in irritability and tenderness of the affected parts. Group A*x* presented 25 per cent x-ray improvement; Group A*y* 66 per cent; Group B*y* 66 per cent. All of Group B*x* improved. Using the above mentioned criteria as evidence of x-ray improvement reveals a higher percentage of improvement in Group B than Group A.

When the same criteria for x-ray evidence of improvement in Group B is applied to Groups S, T and M, a respective 60, 80 and 60 per cent improvement is observed.

Gastric Secretory Response:—The methods for determining the free hydrochloric acid and total acidity were previously described under "Procedures". Case 11 had been subtotally gastrectomized and on gastric analysis was found not to have any free hydrochloric acid in any of the extracted specimens. He is therefore not included in the tabulations of gastric analysis. The determinations were made separately on Group A and Group B using 1 mg. of Tropinox on *all* of these patients during the second part of the "secretory response" studies. The doses used on Groups S, T and M were as mentioned under "Procedures".

The gastric residue determinations were made on specimens extracted before any histamine was given subcutaneously or Tropinox injected through the Levin tube. It is therefore noteworthy that the secretory suppression of free hydrochloric acid of 88, 76, 64, 45 and 57 per cent respectively in Groups A, B, S, T and M were the results of Tropinox treatment. Each patient had taken the last dose between 10 and 12 hours prior to extraction of the residue.

The average free hydrochloric acid at the set times in each group was arrived at by adding the clinical units of that time and dividing the resultant figure by the number of cases in that group. The percentage that the average "With Tropinox" is of the average "Without Tropinox" is determined by dividing the former by the latter. The resultant percentage is subtracted from 100 per cent to determine the percentage of suppression of free hydrochloric acid.

TABLE V

Group	Case	Gastric Residue at 6 Hours		Head of Barium Column at 6 Hours		Tail of Barium Column at 6 Hours	
		Before T	After T	Before T	After T	Before T	After T
Ax	1	N	N	Distal descend. colon	Mid trans. colon	Terminal ileum	Dist. ileal coils
Ax	2	N	N	Rectum	Hepatic flexure	Cecum	Terminal ileum
Ax	3	N	N	Distal ascend. colon	Mid trans. colon	Mid ileal coils	Distal ileal coils
Ax	4	N	N	Splenic flexure	Mid trans. colon	Terminal ileum	Terminal ileum
Bx	8	N	N	Hepatic flexure	Prox. trans. colon	Distal ileal coils	Terminal ileum
Bx	9	N	Y	Dist. trans. colon	Dist. trans. colon	Terminal ileum	Stomach
Bx	10	N	Y	Dist. trans. colon	Dist. ileal coils	Terminal ileum	Stomach
Bx	11	N	N	Dist. ascend. colon	Mid ascend. colon	Terminal ileum	Dist. ileal coils
Ay	5	N	N	Mid trans. colon	Mid trans. colon	Terminal ileum	Terminal ileum
Ay	6	N	N	Rectosigmoid	Mid trans. colon	Terminal ileum	Prox. ileal coils
Ay	7	N	N	Splenic flexure	Mid trans. colon	Ileocecal juncture	Terminal ileum
By	12	N	N	Rectum	Rectum	Cecum	Terminal ileum
By	13	N	N	Rectum	Dist. ileal coils	Terminal ileum	Dist. ileal coils
By	14	N	N	Prox. trans. colon	Dist. ileal coils	Dist. ileal coils	Dist. ileal coils

TABLE V (*continued*)

Group	Case	Gastric Residue at 6 Hours		Head of Barium Column at 6 Hours		Tail of Barium Column at 6 Hours	
		Before T	After T	Before T	After T	Before T	After T
S	15	N	N	Hepatic flexure	Mid trans. colon	Terminal ileal coils	Terminal ileal coils
S	16	N	N	Mid trans. colon	Splenic flexure	Dist. ileal coils	Terminal ileal coils
S	17	N	N	Hepatic flexure	Mid ascend. colon	Dist. ileal coils	Dist. ileal coils
S	18	N	N	Splenic flexure	Mid trans. colon	Dist. ileal coils	Cecum
S	19	N	N	Splenic flexure	Prox. trans. colon	Terminal ileal coils	Terminal ileal coils
T	20	N	N	Dist. trans. colon	Mid descend. colon	Terminal ileal coils	Terminal ileal coils
T	21	N	N	Hepatic flexure	Hepatic flexure	Terminal ileal coils	Cecum
T	22	N	N	Dist. descend. colon	Mid descend. colon	Terminal ileal coils	Terminal ileal coils
T	23	N	N	Hepatic flexure	Prox. descend. colon	Distal ileal coils	Mid ileal coils
T	24	N	Y	Mid ascend. colon	Mid ileal coils	Distal ileal coils	Stomach
		Before Duocotin	After Duocotin	Before Duocotin	After Duocotin	Before Duocotin	After Duocotin
M	25	N	N	Rectum	Mid descend. colon	Cecum	Terminal ileal coils
M	26	N	N	Mid trans. colon	Prox. trans. colon	Mid ileal coils	Dist. ileal coils
M	27	N	N	Mid ascend. colon	Splenic flexure	Terminal ileal coils	Dist. ileal coils
M	28	N	N	Mid descend. colon	Mid trans. colon	Cecum	Dist. ileal coils
M	29	N	N	Dist. descend. colon	Dist. trans. colon	Terminal ileal coils	Terminal ileal coils

Slight gastric residue persisted at the six-hour period of posttreatment x-ray studies in only two patients. These had chronic duodenal ulcers and were taking 1 mg. of the drug while under investigation.

Key: N = None
Y = Yes

The percentages of free hydrochloric acid suppression at the 15 and 30-minute periods were greater in Group B than in Group A. A reversal of the percentages occurred, however, in all of the remaining specimens of these 2 Groups. This may indicate that the effect of Tropinox is less after the first half hour in patients with upper gastrointestinal tract lesions than those with functional gastrointestinal disorders. On the other hand it may indicate that the effect is less after one-half hour in patients having initially higher free hydrochloric acid figures than in those with lower figures and the drug has, therefore, spent itself during the first half hour.

It is interesting to note that the larger dose of Tropinox, as in Group B, used over a short period of time (10 days) apparently had a greater free hydrochloric acid secretory suppression effect than the smaller dose used over a longer period of time (28 days) as particularly in Group T. The gastric analyses of Groups B and T were conducted after 1 mg. of the medicament was introduced into the stomach of each of these patients.

At the 45-90-minute periods the average free hydrochloric acid secretory suppression effect of 1 mg. of Tropinox in Group B is less than 0.5 mg. in the form of Duocotin in Group M. This could be explained in part by the alkaline constituents in Duocotin and in part by some bile regurgitation that developed in Group M during the gastric analyses. It may indicate that an alkaline drug in the dose contained in Duocotin may have a more prolonged effect than an anticholinergic drug in the dose that was used.

It is noteworthy that, even though Group T's gastric analyses were carried out with 1 mg. of Tropinox and Group S's were carried out with 0.5 mg., the percentage of free hydrochloric acid secretory suppression is greater in Group S. This suggests that the method of administration used by Group S has a better effect towards that end than that used by Group T.

Duocotin, in the doses and method of administration used by Group M, appears to have an "over-all" better free hydrochloric acid secretory suppression effect than the effects obtained by Groups S or T.

Conclusions and Comments

A clinical, roentgenological and gastric secretory suppression evaluation of a new medicament having an atropine-like effect is herein reported. There was no intent at this time to compare the effects of this drug, Tropinox alone or when it is in combination with alkaline ingredients (Duocotin), with other medications having anticholinergic properties.

The initial studies were comparative in that the effects of this atropine-brand drug were compared between those obtained on 7 patients that had gastrointestinal functional disorders and 7 patients that had organic lesions.

TABLE VI

Case	Gastric Residue at 24 hours		Head of Barium Column at 24 hours		Tail of Barium Column at 24 hours	
	Before T	After T	Before T	After T	Before T	After T
1	N	N	Rectum	Mid descend. colon	Cecum	Cecum
2	N	N	Rectum	Rectum	Cecum	Cecum
3	N	N	Mid descend. colon	Ascend. colon	Cecum	Cecum
4	N	N	Rectum	Cecum	Sigmoid	Rectum
8	N	N	Rectum	Sigmoid	Ascend. colon	Cecum
9	N	N	Dist. descend. colon	Rectum	Mid trans. colon	Cecum
10	N	N	Rectum	Rectum	Cecum	Cecum
11	N	N	Sigmoid	Rectum	Cecum	Cecum
5	N	N	Rectum	Rectum	Cecum	Cecum
6	N	N	Rectum	Rectum	Cecum	Cecum
7	N	N	Splenic flexure	Cecum	Cecum	Rectum
12	N	N	Rectum	Rectum	Prox. trans. colon	Hepatic flexure
13	N	N	Rectum	Distal descend. colon	Cecum	Cecum
14	N	N	Splenic flexure	Prox. trans. colon	Cecum	Cecum

At 24 hours of x-ray studies none of the patients present any gastric residue. None of the gastrointestinal tracts were free of the contrast barium mixture. Many of the patients had had defecated during the interval of x-ray studies.

Key: N = None

The former, Group A, had less clinical improvement, less side-effects, less over-all x-ray improvement, greater decrease in intestinal motility and greater residue secretory suppression than the latter, Group B. Besides information obtained for academic value the results of this investigation imply that Tropinox in comparable doses is not as effective in functional disorders of the gastrointestinal tract, except for purposes of reducing hypermotility of that tract, as in the presence of actual organic lesions. In the former type of patients the significance of hyperacidity is nondefinitive and probably inconsequential so that the value of a greater secretory suppression quality is practically nullified.

Evaluation of the clinical efficacy of a drug cannot be based alone on whether or not a symptom disappears. The number of symptoms that disappear or subside, the degree of relief of persisting symptoms and the resultant number and degree of side-effects must be considered. Combining these various considerations together with an appreciation that the information obtained was subject to the factors of human errors of both the patients' statements and the investigator's deductions, the conclusions are, nevertheless, that Tropinox in any of the doses used and methods administered is clinically beneficial. Further, this medicament, in the form of Duocotin, using 0.5 mg. 2 hours after each of the 3 main meals and before retiring, as used by Group M, proved to be clinically most effective. When, however, Tropinox was used alone it was clinically most effective in 0.5 mg. dose 1 hour after each of the 3 main meals plus 1 mg. before retiring, as used by Group S.

Approximately the same clinical effects were produced by 1 mg. as by 0.75 mg. taken 1 hour after each of the 3 main meals and before retiring, as used by Groups B*x* and B*y*. Further, their side-effects were greater than those resulting from the other doses tested. Therefore, it is reasonable to conclude that the doses of Tropinox used by Groups S or M are preferable to the larger doses used by Groups B*x*, B*y* or T.

Side-effects were of greater intensity and more frequent when the large dose (1 mg.) was used. Further, side-effects were more frequent in the patients with organic lesions than with functional disorders except for xerostomia. The xerostomia was the most frequent side-effect. Mydriasis, euphoria, difficulty on starting the urinary stream and constipation were other side-effects. None were severe; all tended to reduce in intensity as the study continued; all disappeared immediately upon withdrawal of the drug.

During an investigation, as herein reported, relating to the effects of a medicament on the gastrointestinal tract as evidenced on x-ray studies several factors must be considered: a. Since the clinical trials resulted in clinical influence on the peptic ulcers, the x-ray findings were, undoubtedly, also influenced by the doses of the drug and methods of administration during the 10- and 28-day periods. The "immediate" effects, however, of the varying doses as

TABLE VII

Group	Case	Residue Free HCl		Residue Total Acidity	
		B	A	B	A
Ax	1	0	0	18	10
Ax	2	5	0	14	10
Ax	3	22	3	40	20
Ax	4	30	0	52	18
Ay	5	10	0	32	18
Ay	6	2	0	8	0
Ay	7	48	12	60	38
Bx	8	40	19	55	37
Bx	9	18	0	30	5
Bx	10	33	20	45	32
By	12	18	0	20	30
By	13	48	0	63	20
By	14	0	0	11	10
S	15	24	8	54	24
S	16	22	14	48	42
S	17	59	26	85	60
S	18	38	10	54	22
S	19	38	8	54	18
Average		36.2	13.2	59.0	33.2
T	20	16	12	36	28
T	21	8	4	18	20
T	22	40	26	62	40
T	23	0	0	10	12
T	24	12	0	28	14
Average		15.2	8.4	30.8	22.8
M	25	33	5	61	20
M	26	16	4	28	20
M	27	28	20	52	36
M	28	68	20	100	42
M	29	126	68	130	96
Average		54.2	23.4	74.2	42.8

The second gastric residue "A" was extracted 10 to 12 hours after the last dose of Tropinox had been taken. Note that the figures indicate acid suppression activity of the medicament during that interval. Case 11 is not included because he had been subtotally gastrectomized and had no free hydrochloric acid at any time.

Key: B = Before taking the medicament.
A = After taking the medicament.
Figures are expressed in clinical units.

TABLE VIII

Group	# Case	Dia.	FREE HYDROCHLORIC ACID (Clinical Units)												TOTAL ACIDITY (Clinical Units)											
			15 min.		30 min		45 min.		60 min.		75 min.		90 min.		15 min.		30 min		45 min.		60 min.		75 min.		90 min.	
			B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
Ax	1	NL	19	0	52	2	50	3	42	10	30	6	20	2	45	8	60	10	54	10	50	22	36	18	30	8
Ax	2	NL	28	6	40	11	52	20	64	17	54	14	38	11	41	14	58	22	64	32	82	27	67	22	50	19
Ax	3	NL	24	12	44	36	36	38	34	34	29	30	16	18	40	24	68	52	56	54	50	48	40	42	28	30
Ax	4	NL	20	23	40	38	45	55	36	42	0	34	0	26	60	40	48	52	62	72	58	60	11	48	7	37
Ay	5	NL	14	2	28	10	32	14	34	16	36	18	28	15	40	21	55	38	56	40	59	40	59	40	50	38
Ay	6	NL	22	0	48	10	56	22	50	30	42	30	38	28	38	0	60	26	74	40	62	58	54	50	46	37
Ay	7	NL	54	18	62	27	70	38	58	26	46	20	40	20	68	38	74	72	78	55	68	40	58	32	52	30
Average			25.8	8.71	44.8	19.1	48.7	27.1	45.4	27.0	33.8	21.7	25.7	17.1	47.2	20.7	60.4	34.5	63.4	43.2	61.2	42.1	46.4	36.0	37.5	28.4
Bx	8	OL	46	23	58	34	55	36	50	26	48	18	44	15	60	40	85	49	78	49	66	42	52	30	52	26
Bx	9	OL	20	12	28	20	39	54	44	30	39	20	30	20	36	42	40	51	58	76	52	42	56	48	50	46
Bx	10	OL	55	10	78	23	87	40	65	44	48	28	35	20	64	13	87	38	96	56	71	52	62	40	52	32
By	12	OL	22	10	54	18	60	26	50	32	23	17	18	11	24	34	58	36	64	40	52	42	28	40	20	21
By	13	OL	63	0	70	12	42	26	38	30	18	30	13	28	82	20	92	30	55	36	52	44	34	48	26	48
By	14	OL	26	12	30	16	36	28	48	52	37	42	30	36	40	30	44	38	48	52	60	78	52	60	44	54
Average			38.6	11.1	53.0	20.5	53.1	35.0	49.1	35.6	35.5	25.8	28.3	21.6	51.0	29.8	67.6	40.3	66.5	51.5	58.8	50.0	47.3	44.3	40.6	37.8

TABLE VIII (*continued*)

Group	Case #	Dia.	FREE HYDROCHLORIC ACID (Clinical Units)												TOTAL ACIDITY (Clinical Units)											
			15 min.		30 min		45 min.		60 min.		75 min.		90 min.		15 min.		30 min		45 min.		60 min.		75 min.		90 min.	
			B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
S	15	D-U	30	20	38	30	58	42	76	48	60	60	54	54	60	35	66	42	76	58	108	70	86	76	80	78
S	16	D-U	50	30	92	66	122	80	160	68	132	52	112	50	76	54	116	96	148	100	178	82	150	76	130	76
S	17	D-U	82	66	106	78	132	92	165	100	166	110	162	100	102	82	120	92	150	112	181	120	186	120	184	110
S	18	D-U	44	16	56	28	52	34	48	42	44	50	42	46	58	35	70	40	66	52	62	60	54	66	50	62
S	19	D-U	50	12	56	22	60	34	76	52	84	66	72	70	66	24	74	40	81	54	88	68	98	70	90	82
Average			51.2	28.8	69.6	44.8	84.8	56.4	105.0	62.0	97.2	67.6	88.4	64.0	72.4	46.0	89.2	62.0	104.2	75.2	123.4	80.0	114.8	81.6	106.8	81.6
T	20	D-U	54	24	67	66	88	76	96	78	104	88	102	92	74	40	89	80	104	92	112	96	116	100	110	110
T	21	D-U	28	22	34	35	38	42	52	50	38	42	32	38	42	30	46	52	50	60	62	68	54	58	42	54
T	22	D-U	50	46	78	68	86	84	92	98	76	100	62	92	62	58	94	88	100	100	102	108	92	110	82	100
T	23	D-U	30	12	68	14	72	48	70	44	68	54	62	54	52	26	80	50	100	64	88	60	88	70	78	68
T	24	D-U	30	26	64	36	66	42	72	50	78	54	74	48	46	38	76	44	80	60	84	68	90	70	90	68
Average			38.4	26.0	62.2	43.8	70.0	58.4	76.4	64.0	72.8	67.6	66.4	64.8	55.2	38.4	77.0	62.8	86.8	75.2	89.6	80.0	88.0	81.6	80.4	80.0
M	25	D-U	61	32	70	34	74	18*	68	12*	64	4*	50	4*	92	44	96	48	104	24*	100	22*	88	18*	80	16*
M	26	D-U	22	10	30	14	39	18	46	14	38	14	30	12	34	28	42	30	56	34	54	28	50	22	46	18
M	27	D-U	72	88	140	108	164	96	168	98	152	78	144	70	86	100	178	122	180	102	182	104	164	86	156	82
M	28	D-U	102	48	148	64	170	88	158	76	142	72	128	82	124	70	166	80	184	104	172	82	160	82	142	98
M	29	D-U	56*	42	96*	56	102	78	84	82	134	50*	118	24*	68*	56	112*	66	122	88	100	90	152	62*	140	30*
Average			62.6	44.0	96.8	55.2	109.8	59.6	104.8	56.4	106.7	43.6	94.0	38.4	80.8	59.6	118.8	69.2	129.2	70.4	121.6	65.2	122.8	54.0	112.8	48.8

There is evidence that suppression of acid secretion during the first half hour is greater in organic lesions than functional disorders. Beyond that period a reversal of that activity develops.

Key: Dia. = Diagnosis
NL = Functional disorder
OL = Organic lesion
B = First fractional analysis when the medicament was not used.
A = After the study and the medicament was orally used prior to the injection of histamine.
* = Bile regurgitation
D-U = Duodenal ulcer

outlined in "Procedures" could only be brought into view by using the drug at a standard time prior to and during the posttreatment x-ray investigation. b. "Time" x-raywise refers to the interval from the period of ingestion of the barium meal up to the period when the film is taken and/or fluoroscopy is carried out. Therefore, it can be appreciated that intestinal motility as judged by x-ray evidence will, undoubtedly, be influenced in part by the rate of gastric emptying which in turn could be affected in varying degrees by the presence of pylorospasms as well as by actual disease in the immediate area.

The 0.5 mg. dose of Tropinox, as used by Group S had the greatest favorable effect upon reducing the incidence of pylorospasms. It produced a 60 per cent reduction in pylorospasms from the pre- to the posttreatment x-ray study. The 1 mg. dose had no appreciable favorable effect on the pylorospasms of Group Bx and resulted in only a 20 per cent reduction in the number of patients of Group T that were so affected during the pretreatment study.

The 0.5 mg. dose of Group S completely eliminated gastric residue at the 3-hour study. The 1 mg. dose revealed an increase in gastric residue at the 3-hour study in Groups Bx and T and was the only dose to evidence gastric residue in some of its 6-hour studies. The "Duocotin-patients" of Group M revealed no change in the 3-hour gastric residue findings. The 1 mg. and 0.75 mg. doses were about equally effective in reducing intestinal motility; the 0.5 mg. dose had at most a moderate effect towards that end.

Using the criteria for x-ray improvement as outlined in "Observations" one must conclude that the greatest over-all improvement as evinced on x-ray was obtained with the 1 mg. dose as in Groups Bx and T. One must, however, consider from clinical information and the pretreatment x-ray evidence what is intended to be accomplished before deciding what would be the best dose to use in any one particular case. This is illustrated by using 0.5 mg. to reduce pylorospasms but employing 1 mg. in cases of gastrointestinal hypermotility.

Gastric secretory analyses are influenced by many factors besides the dose of the medicament under study. These factors warrant consideration when the over-all effect of the drug is evaluated: a. Emotional tension increases gastric secretion of free hydrochloric acid. b. Swallowing of saliva and/or regurgitation of bile into the stomach decreases the degree of acidity by direct chemical neutralization. c. Gastroduodenal lesions may result in hypo- or hyperacidity. d. Varying gastric secretory activities are often observed in the same patient under standardized conditions both as to degrees of acidity and volumes secreted.

It is conceded that all of the aforementioned factors might be reduced in their effects by using the methods employed by Ihre[2] and by Sun, Shay and Ciminera[3] in their studies on *basal* gastric secretions. This report, however, is

intended as a study employing average standards that can be used for practical purposes under circumstances approximating those daily experienced by patients.

In reporting an evaluation of gastric analysis figures resulting from medicinal effects it behooves the investigators to include with the figures: a. when the effect developed and b. for what length of time the effect was sustained. If these 2 factors are not included, incorrect deductions could easily be reached by the clinician, who understandably depends upon the investigator's reports for evaluation.

The gastric analyses were conducted as described under "Procedures". The posttreatment analyses must be considered as being influenced in part by the doses of the medicament and the methods of administration as well as the doses used for determination of "immediate" effects. Special consideration must be borne in mind for the effects of Duocotin on gastric secretion since that medicament contains, along with Tropinox, component parts that are alkaline and, therefore, chemical antacids.

It was noted on analyses of the posttreatment residue specimens that Tropinox has a suppression effect on free hydrochloric acid secretion for 10 to 12 hours. The 1 mg. dose produced a greater percentage of residue-free hydrochloric acid secretory suppression in Groups A or B than did the smaller doses in Groups S or M. When the dose used was 1 mg. twice daily, the suppression effect was less than when a total of 2.5 mg. were used daily, as in Group S. Since the dose taken before retiring was the same for each of these Groups, the conclusion drawn is that the total daily dose and method of administration does influence in part the acid secretory suppression effect for as long as 10 to 12 hours.

The secretory suppression effect is of longer duration when Duocotin is used, as in Group M, than when Tropinox is used in the other tested doses and methods of administration.

From the results of the series herein reported one concludes that the atropine-brand medicament studied has good free hydrochloric acid suppression effect. Further, 0.5 mg. of the drug when in combination as in Duocotin and taken 2 hours after breakfast, lunch and dinner and before retiring produces the most satisfactory *over-all* effects as compared to the other doses and methods of administration tested in this survey.

The author acknowledges that longer evaluation periods are indicated before a final conclusion could be deduced. It is appreciated that 29 patients is too small a series for final conclusions. The observations, however, suggest that Tropinox will prove to be an effective agent where suppression of free hydrochloric acid secretion, reduction of gastrointestinal motility and anticholinergic relief from gastrointestinal symptoms is indicated. This medicament

TABLE IX

Average Free HCl (Clinical Units) of Cases With *No* Lesions (Group A)				Average Total Acidity (Clinical Units) of Cases With *No* Lesions		
Time	Without Tropinox	With Tropinox	% of HCl secretory suppression	Time	Without Tropinox	With Tropinox
Residue	16.71	2.14	88%	Residue	32.00	16.28
15 minutes	25.85	8.71	67%	15 minutes	47.42	20.71
30 minutes	44.85	19.14	58%	30 minutes	60.42	34.57
45 minutes	48.71	27.14	45%	45 minutes	63.42	43.28
60 minutes	45.42	27.00	45%	60 minutes	61.28	42.14
75 minutes	33.85	21.71	36%	75 minutes	46.42	36.00
90 minutes	25.71	17.14	34%	90 minutes	37.57	28.42

With Lesions (Group B)				*With* Lesions		
Time	Without Tropinox	With Tropinox	% of HCl secretory suppression	Time	Without Tropinox	With Tropinox
Residue	26.16	6.50	76%	Residue	37.33	22.33
15 minutes	38.66	11.16	72%	15 minutes	51.00	29.83
30 minutes	53.00	20.50	62%	30 minutes	67.66	40.33
45 minutes	53.16	35.00	35%	45 minutes	66.50	51.50
60 minutes	49.16	35.66	28%	60 minutes	58.83	50.00
75 minutes	35.50	25.83	28%	75 minutes	47.33	44.33
90 minutes	28.33	21.66	24%	90 minutes	40.66	37.83

TABLE IX (*continued*)

Average Free HCl (Clinical Units) of Cases in Group "S"				Average Total Acidity (Clinical Units) in Group "S"		
Time	Without Tropinox	With Tropinox	% of HCl secretory suppression	Time	Without Tropinox	With Tropinox
Residue	36.2	13.2	64%	Residue	59.0	33.2
15 minutes	51.2	28.8	44%	15 minutes	72.4	46.0
30 minutes	69.6	44.8	36%	30 minutes	89.2	62.0
45 minutes	84.8	56.4	34%	45 minutes	104.2	75.2
60 minutes	105.0	62.0	41%	60 minutes	123.4	80.0
75 minutes	97.2	67.6	31%	75 minutes	114.8	81.6
90 minutes	88.4	64.0	28%	90 minutes	106.8	81.6
Group "T"				Group "T"		
Residue	15.2	8.4	45%	Residue	30.8	22.8
15 minutes	38.4	26.0	33%	15 minutes	55.2	38.4
30 minutes	62.2	43.8	30%	30 minutes	77.0	62.8
45 minutes	70.0	58.4	17%	45 minutes	86.8	75.2
60 minutes	76.4	64.0	17%	60 minutes	89.6	80.0
75 minutes	72.8	67.6	8%	75 minutes	88.0	81.6
90 minutes	66.4	64.8	3%	90 minutes	80.4	80.0
Group "M" (Duocotin was used)				Group "M" (Duocotin was used)		
Residue	54.2	23.4	57%	Residue	74.2	42.8
15 minutes	62.6	44.0	30%	15 minutes	80.8	59.6
30 minutes	96.8	55.2	43%	30 minutes	118.8	69.2
45 minutes	109.8	59.6	46%	45 minutes	129.2	70.4
60 minutes	104.8	56.4	47%	60 minutes	121.6	65.2
75 minutes	106.0	43.6	59%	75 minutes	122.8	54.0
90 minutes	94.0	38.4	60%	90 minutes	112.8	48.8

The residue specimens were extracted before the Tropinox was orally administered for the balance of the analyses studies. Note that the secretory acid suppression was greater for the first half hour in those patients with organic than those with functional disorders. Beyond that period a reversal of that activity developed. In Group "M" bile regurgitated in Case 25 "With Duocotin" at 45, 60, 75, and 90 minutes, and Case 29 "Without Duocotin" at 15 and 30 minutes, and "With Duocotin" at 75 and 90 minutes.

is more favorably effective in the presence of gastrointestinal lesions than in functional disorders of that tract.

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CLINICAL EVALUATION OF MONODRAL IN THE TREATMENT OF GASTROINTESTINAL DISEASES*

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Recent reports[1-11] on the use of Monodral bromide† for the control of parasympathetic overstimulation of the gastrointestinal tract have encouraged the author to study its effect in the treatment of gastrointestinal disorders over a period of approximately 30 months. Results have been encouraging and this new and major advance in oral anticholinergic therapy warrants a preliminary report at this time.

The use of an oral anticholinergic as a helpful adjunct in the total therapeutic regime involves no new principle in the therapy of certain gastrointestinal disorders and accordingly Monodral is recommended only as one of the superior therapeutic agents in the control of parasympathetic overstimulation. Other methods of treatment, such as the use of antacids, dietary management, rest and surgical intervention, should be used when indicated.

Monodral is an anticholinergic compound which laboratory and clinical investigations have demonstrated to be more effective than earlier anticholinergics[1-11]. It is a potent, well tolerated anticholinergic for peptic ulcer (gastric and duodenal), hyperacidity, gastritis, pylorospasm, gastrointestinal hypermotility, spastic and irritable colon. Monodral produces marked inhibition of gastric secretion frequently to the point of anacidity and it causes powerful reduction of hypermotility and spasm of the stomach and small intestine. Rapid relief from pain favors ulcer healing.

Pharmacology

Monodral bromide is 2-diethylaminoethyl 2-cyclopentyl-2-(2-thienyl)hydroxyacetate methobromide, a white crystalline powder soluble in water to the extent of at least 20 per cent.

Monodral blocks vagal stimulation of smooth muscle of the gastrointestinal tract and inhibits gastric secretion and motility. A comprehensive comparison of the ability of various antispasmodic compounds, including Monodral, atropine sulfate and atropine methylnitrate, to reduce or abolish the effects of parasympathetic stimulation showed that Monodral was the most active cholinolytic compound against carbachol-induced vasodepression, salivary secretion and intestinal motility of the barbitalized dog[3].

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*Read by title at the Second Annual Convention of the American College of Gastroenterology, Chicago, Ill., 24, 25, 26 October 1955.

†Monodral bromide, brand of penthienate bromide, Winthrop Laboratories, Inc.

In a series of 16 compounds evaluated for anticholinergic activity Monodral was one of the three most effective agents in controlling the gastrointestinal secretion and hypermotility with reduction in pain and subsequent promotion of healing[1]. In addition 5 to 10 mg. of Monodral produced anacidity in 7 of 11 patients which persisted from 3 to 5 hours[1]. Balloon-kymographic and radiographic studies showed consistent depressed gastric and small intestine motor activity with oral doses of 5 to 20 mg. of Monodral[4,6]. In patients with irritable or spastic colon there was good to excellent relief of cramps, diarrhea, abdominal rumblings, and excess mucus secretions in 23 of 29 cases[6].

Method of Study

The drug was administered orally in tablets or as an elixir in combination with appropriate diets, with sedatives such as Mebaral, with analgesics and with antacids when indicated. All patients were private ambulatory cases. Each was given a complete clinical investigation which included a detailed history, physical and laboratory examinations, and appropriate roentgen examination. Endoscopic examinations were made in all cases to confirm the presence of esophageal and/or gastric disease.

Monodral was given to each patient in the form and dosage deemed best suited to the individual case on the basis of previous experience with other drugs of a similar nature. No comment of any kind was offered to the patient as to the relative effectiveness of the drug so as not to induce suggestion. Written instructions on the taking of the medication were given so that maximum effectiveness could be obtained. Patients were followed-up at regular intervals, usually every week or two, in order to check symptomatic response and objective signs of improvement. No comments were offered as to expected results and no leading questions relative to side-effects were given as these should come from the patient voluntarily. Later on in the course of the treatment, however, patients were asked if they experienced any of the unpleasant side-effects which are most apt to occur with anticholinergic drugs, such as dryness of the mouth, blurring of vision, difficulty with urination and constipation.

Criteria of clinical responses are admittedly difficult to appraise, but the advantages of prolonged periods of personal observation with clinical laboratory tests and with follow-up roentgen and endoscopic examinations whenever possible serve as fairly reliable guides or indices as to the efficacy of a therapeutic agent. Unfortunately different methods of reporting preclude the possibility of accurate statistical analysis, but it appears reasonably conservative to assert that the vast majority of patients who receive full therapeutic doses of effective anticholinergic agents for definite indications will derive benefits. Significant improvement of functional and objective evidence is seen with sufficient frequency in patients treated with Monodral to justify continued investigation of its anticholinergic properties.

The effectiveness of the anticholinergic drugs in inducing remissions in benign peptic ulceration of the digestive tract has been reported by a great many investigators[1-11]. Proper ulcer therapy, however, requires a physician who understands the use and methods he prescribes, and a patient sufficiently informed of his condition and the treatment so that he can play a successful part in the medical drama.

Since the exact etiology of ulcers has remained obscure, their cure remains an enigma. A perverted physiology, however, precipitated by neurohumoral imbalance mediated through the dorsal vagal nuclei and nerves activates the gastric secretory mechanism to produce more than normal hydrochloric acid and pepsin, which in a susceptible mucous membrane produces erosions and ulcerations. Since Monodral is a pharmacologically potent and dependable parasympathetic blocking agent by effecting inhibition of neural stimuli at the ganglion and effectors where the presence of acetylcholine mediates the transmission of stimuli the rationale for its use for the treatment of ulcers is well founded.

The immediate results of standard conservative management for uncomplicated peptic ulcer, which usually consists of bland diets, antacids, etc., are satisfactory in approximately 80 per cent of patients for short periods of time. Recurrence of symptoms occurs, however, in 6 to 12 months in about 75 per cent of patients. In the first two or three years of the ulcer antacids and dietary measures usually give temporary satisfactory relief to the patient along with a false sense of security, even though recurrences are frequent. After three or four years recurrences are more frequent and more severe, without the usual relief of pain with diet and antacids. The current emphasis on the alternations of the gastric acidity, hypersecretion and spasm with the use of effective anticholinergic drugs in connection with peptic ulceration has been justified in terms of improved therapy. In order to appraise newly suggested remedies for the treatment of peptic ulceration, several methods of clinical assay are available. They include the rate of symptomatic response, the rate of healing and the remote results observed over a period of years.

Clinical Results

Patients with positively identified ulcers of various types and degrees of severity were treated with Monodral in order to study the physiological effect of the drug. All patients were ambulatory and had a history of ulcer-like distress for a few years, the majority receiving previously some conventional and conservative type of ulcer management and treatment of hyperacidity. Several had received other anticholinergic agents. A modified bland diet with adequate calories, vitamins, minerals, etc., with the usual restrictions and antacids in the early part of treatment for patient comfort until the anticholinergic effects were adequately controlling the spasm and acidity. Oral administration is necessary

TABLE I

DUODENAL ULCER—TREATED WITH MONODRAL

				Treatment			Results		
No.	Age	Sex	Duration Symptom	Started	Completed	Side-effects	Immediate	6 Mo.	1 yr.+
1	48	F	6 yrs.	3/54	4/55	0	good	good	good
2	46	M	10 yrs.	3/53	7/54	+	fair	good	good
3	47	M	8 yrs.	5/53	8/53	0	fair	good	recurrence (1954)
4	39	M	4 yrs.	4/53	8/53	+	good	good	died 9/54 w/cancer
5	45	M	5 yrs.	4/53	7/53	0	good	good	good
6	59	M	8 yrs.	5/53	5/53	+	good	retreated	good
7	60	M	6 yrs.	9/53	12/53	0	good	good	recurrence retreated
8	46	M	10 yrs.	6/53	9/53	+	good	good	recurrence 3/55
9	23	M	2 yrs.	3/54	6/54	0	good	good	good
10	55	M	8 yrs.	4/54	7/54	0	good	good	good
11	50	M	4 yrs.	10/54	1/55	0	good	good	good
12	44	M	6 yrs.	4/53	7/53	0	good	good	good
13	40	M	9 yrs.	1/54	5/54	+	fair	good	—
14	54	M	5 yrs.	7/54	10/54	0	good	good	good
15	54	M	3 yrs.	8/53	11/53	0	good	good	good
16	50	M	4 yrs.	4/54	7/54	0	good	good	good
17	51	F	7 yrs.	6/54	8/54	0	good	good	retreated 7/55
18	47	M	6 yrs.	10/53	1/54	0	good	good	good
19	51	M	5 yrs.	9/53	12/53	0	good	good	good
20	40	F	6 yrs.	11/54	1/55	+	good	good	—
21	38	F	12 yrs.	4/54	7/54	++	fair	fair	good

TABLE I (*continued*)

				Treatment			Results		
No.	Age	Sex	Duration Symptom	Started	Completed	Side-effects	Immediate	6 Mo.	1 yr.+
22	45	M	2 yrs.	12/54	3/55	+	good	good	—
23	53	M	6 yrs.	4/53	7/53	0	good	good	death sud. coronary 6/55
24	62	M	18 yrs.	5/53	8/53	0	good	good	good
25	47	M	4 yrs.	1/54	4/54	0	good	good	good
26	56	M	5 yrs.	10/53	1/54	0	fairly good	good	good
27	32	F	4 yrs.	11/52	2/53	0	good	good	good
28	56	M	7 yrs.	2/53	3/53	0	good	retreated	good
29	48	M	15 yrs.	12/52	3/53	++	fair	fair	good
30	47	F	12 yrs.	11/52	2/53	0	good	good	no response to follow-up
31	38	M	8 yrs.	1/53	3/53	0	good	retreated	good
32	42	M	6 yrs.	5/53	8/53	0	good	good	good
33	45	M	10 yrs.	3/53	6/53	0	good	good	good
34	28	M	4 yrs.	4/53	6/53	+	good	good	retreated
35	36	F	5 yrs.	7/53	10/53	0	good	good	good
36	34	M	6 yrs.	3/53	5/53	+	good	good	retreated
37	62	F	12 yrs.	4/53	8/53	0	good	good	good
38	44	M	10 yrs.	3/53	5/53	0	good	retreated	retreated
39	52	M	8 yrs.	4/53	6/53	0	fairly good	good	retreated
40	35	M	2 yrs.	4/55	7/55	+	good	—	—
41	28	M	2 yrs.	7/54	9/54	0	good	good	good

Five other patients were started on treatment with Monodral or Monodral with Mebaral but stopped treatment on their own accord for various reasons after only 2 or 3 weeks of treatment. Three of the patients stopped the treatment because of dry mouths, blurred vision, etc., from the drug.

for practical application and when it is given on a fasting stomach it is definitely more effective. I feel that the curtailment of motility is as important as the antisecretory influence.

Benign Gastric Ulcer

The following case histories are typical of the effect of Monodral in the treatment of benign gastric ulcer.

Case 1:—Mrs. C. C., a 48-year old female, had recurring episodes of epigastric distress with gas and occasional nausea for the past 5 years. None of the attacks were very annoying nor of too long duration until January 1955. Past history revealed a hysterectomy for fibroids in 1953, appendectomy, and two attacks of cystitis in the past two years. The epigastric distress which had started in January gradually became more annoying with variable relief from food and from some proprietary medication taken for the relief of so-called indigestion. X-rays of the gallbladder, colon, chest and urinary tract were essentially negative. X-rays of the upper gastrointestinal tract revealed considerable antral spasm and so-called hypertrophy of the gastric mucosa, particularly in the lower third. A test meal with aspiration in one hour revealed 60 c.c. of gastric residue with F.A. 30/T.A. 56 and a trace of occult blood. Gastroscopic examination revealed a stomach generally quite hypertonic especially in the lower third. The antrum was gradually distended and peristalsis traversed uninterrupted to the pylorus. There was no evidence of antral or pyloric ulcer. Examination of the fundus with the retrograde scope revealed a benign appearing ulcer approximately 1 x 1.5 cm. on the posterior wall 4 cm. below the cardia.

Treatment was started 13 April 1955 with a bland diet, vitamins and Monodral 5 mg. q.i.d., a.c. and h.s. Antacids were used for the first 10 days to control erosion until the anticholinergic effects were well established. The patient became more comfortable after the first 24 hours and she became completely symptom-free at the end of one week. Diet was liberalized at the end of two weeks with qualitative restrictions after one month. Monodral was continued on the same doses until 13 July 1955 when a repeat gastroscopic examination disclosed complete healing of the ulcer. Pregastroscopic examination of the stomach gave only 8 c.c. fasting gastric residue with no F.A. during the 3 weeks of treatment and after the 4th week practically none. Constipation, which had been present to some extent over the past 3 years, became somewhat more marked after the change in diet and medication, but it was difficult to say if this was attributable to the anticholinergic effect of the Monodral. The addition of a bland methylcellulose preparation corrected the constipation. The patient is continuing on 2.5 mg. of Monodral a.c. and 5 mg. h.s. with a liberal diet and no side-effects. Bowels are regular without any correctives.

Case 2:—Mrs. E. R. B., a 38-year old female drug store clerk, began to experience gnawing hunger distress in the midepigastrium one to two hours

p.c. which was associated with gas and occasional nausea. These symptoms started in 1944 following the care of a seriously ill member of the family. Recurrences took place once or twice a year for the first few years and in 1951-53 the attacks occurred more frequently with increasing severity so that the patient became more nervous and lost weight. The patient had a hysterectomy and appendectomy in 1950. She had an asthenic build with a weight of 98 lbs. There was a definite epigastric tenderness and no palpable masses. Clinical laboratory tests were all normal: blood sugar 98 mg. per cent; N.P.N. 32 mg. per cent; sedimentation rate 8 mm./h.; Kahn neg.; Undulant aggl. neg.: hemoglobin 13 gm.; R.B.C. 4.2 million; Urine neg.; B.M.R. minus 6 per cent; chest x-ray neg.; gastric analysis at 1 hour F.A. 34/T.A. 56 with a faint trace of occult blood. An upper gastrointestinal series showed gastric mucosal changes through the *pars media* and antrum with a suggestion of gastric mucosal prolapse through the pylorus. A gastroscopy on 16 February 1953 revealed a spastic antrum with granular mucosa and a posterior wall benign ulcer proximal to the angulus approximately 1 cm. in diameter.

Treatment was instituted with a relatively liberal bland high caloric diet, vitamin supplements and 2½ mg. of Monodral q.i.d., a.c. and h.s. Antacids were given for the first 2 weeks. The patient became symptom-free after the first week, felt much better generally and gradually gained weight. There was no intolerance to the medication nor were side-effects noted to any degree. A repeat gastroscopic examination was done at the conclusion of the first 13 weeks of treatment and it revealed a completely healed ulcer, the stomach was not hypertonic, peristalsis was normal, and the general appearance of the mucosa was normal. The diet has been so liberalized that in variety and caloric content it is general, since only a few foods are restricted including coffee. For the past year the patient has held to a weight of 116 to 119 lbs. Although symptom-free she has continued to take Monodral prophylactically 2.5 mg. a.c. and 5 mg. h.s. to the present.

Table I shows the results of therapy with Monodral for 41 patients with duodenal ulcer and Table II shows the results for 11 patients with gastric ulcers.

As is usual in a gastrointestinal practice, there are certain groups of patients who present symptoms suggestive of peptic ulcers with epigastric tenderness and with symptomatic hyperacidity as shown by some excess secretion and acidity on gastric analysis, but by all available morphologic methods of examination demonstrate no findings of ulcers even when followed carefully for years. Certain patients in this group, however, have roentgen findings of duodenitis, gastritis, or some abnormal spastic condition and usually hypermotility. Endoscopically findings not revealed by x-ray may be apparent. Esophagoscopy may reveal the presence of a peptic esophagitis or an occult hiatus hernia. The gastroscopic examination may reveal at times a superficial or hypertrophic gastritis, increased gastric tonicity, spasm especially antral and pylorospasm. In spite of no definite or demonstrable ulceration, most of these patients improve

remarkably with Monodral. Effective therapy requires a skillful evaluation of the physiologic and emotional factors involved. Specific details of treatment should be adjusted to the needs of the individual, but certain principles are generally applicable. It is essential to first relieve the patient's anxiety concerning the possibility of serious organic disease. This is best accomplished by a careful and complete examination, as described above.

TABLE II

GASTRIC ULCER—TREATED WITH MONODRAL

				Treatment			Results		
No.	Age	Sex	Duration Symptom	Started	Completed	Side-effects	Immediate	6 Mo.	1 yr.+
1	62	M	6 yrs.	12/52	3/53	0	good	good	good
2	35	M	4 yrs.	3/53	5/53	++	poor	oper.*	
3	42	F	5 yrs.	4/53	7/53	0	good	good	good†
4	43	F	7 yrs.	4/53	7/53	+	fair	good	good
5	58	F	10 yrs.	5/53	8/53	0	fair	good	good
6	42	M	8 yrs.	9/53	12/53	0	good	good	good
7	55	F	4 yrs.	6/54	9/54	0	good	good	good
8	51	M	6 yrs.	1/54	4/54	+	good	good	good‡
9	37	F	5 yrs.	10/54	1/55	0	good	good	
10	51	M	8 yrs.	9/53	12/53	0	good	good	good
11	48	F	2 yrs.	1/53	4/53	0	good	good	

*Operation in May 1953 showing a deep benign penetrating ulcer on the posterior wall against the pancreas.

†Ulcer healed gastroscopically in 8 weeks and the patient continued to take 2.5 mg. of Monodral.

‡Patient continues to take Monodral regularly.

All cases were verified by gastroscopy as having benign ulcers. All patients, except No. 2 were rescoped in 3 to 4 months showing that the ulcers had completely healed.

A group of 85 patients were treated who could be classified in this general group and they were distributed as follows: gastrojejunal ulcer, 1; esophageal ulcer, 2; duodenitis, 7; hypertrophic gastritis, 8; peptic esophagitis, 7; biliary dysfunction or dyskinesia, 12; neuromuscular imbalances, 12 with spasm of the distal segment of the stomach and 33 with functional disturbance of the colon.

In addition to diets adjusted to each individual's need, Monodral was given either in tablet or elixir form a.c. and h.s. from two weeks to several

months depending on the individual need and tolerance. Inasmuch as one drug is often used to potentiate the action of another, the combination of the anticholinergic Monodral with Mebaral*, which is a reliable sedative and antispasmodic, has been a most successful drug for controlling the emotional disturbances as well as the spasticity of these conditions. During the course of treatment 60 per cent of this group of patients received this combination of Monodral and Mebaral at some time with effective results. In those whom follow-up studies have been sufficient for clinical evaluation, 80 per cent of these patients have been definitely benefited by Monodral alone and/or the combination of Monodral with Mebaral, when they were taken over a period of time sufficient to allow the patient to make the necessary physiological adjustments. Minor side-effects, such as drying of the mouth, were noted in a slightly higher incidence (8 to 10 per cent) in this group than in the known ulcer group. Apparently neurogenic factors are a great deal more in preponderance here than in the ulcer group.

Case 3:—A 62-year old male had a gastroenterostomy in 1943 with recurrences of abdominal distress off and on at irregular intervals. Roentgen and gastroscopic evidence showed a gastrojejunal ulcer. Treatment was started with Monodral in December 1954 and continued for 16 weeks. There was slight dryness of the mouth the second and third week, but this disappeared and the medication was thereafter well tolerated. There have been no signs of recurrence.

Esophageal Ulcers and Esophagitis

Case 4:—A 62-year old female with a previous gallbladder removal, appendectomy, and hysterectomy had a high epigastric pain with no roentgen evidence of ulcer. Esophagoscopy and gastroscopy revealed esophagitis, esophageal peptic ulcer and a small posterior wall gastric ulcer in March 1955. Treatment of Monodral with Mebaral b.i.d. for 14 weeks gave marked relief and was well tolerated.

Case 5:—A 58-year old male had epigastric distress and burning extending into the chest for several years. X-ray showed a spastic distal esophagus and esophagoscopy demonstrated an esophageal ulcer in May 1955. A dose of 5 mg. of Monodral q.i.d. was given for 15 weeks with diet and antacids for the first three weeks. There was symptomatic improvement and esophagoscopic examination showed the ulcer healed. Four months later there was some scarring and constriction which had to be dilated once. There has been no recurrence of symptoms to date.

In esophagitis there may be high epigastric and retrosternal distress and pain of irregular frequency, duration and response to food and medications such as antacids. The usual clinical and roentgen examinations of the chest, gall-

*Mebaral® (brand of mephobarbital), Winthrop Laboratories, Inc.

bladder and upper gastrointestinal tract are not very revealing. Most of these cases are regurgitators with some patients having a small sliding hiatus hernia, pylorospasm, etc. All have a normal or high gastric acidity. There is tenderness in the lower esophagus which is due to the regurgitation of acid gastric juice. There were 7 patients in whom this acid-peptic corrosive esophagitis was diagnosed by esophagoscopy. There were 5 females and 2 males ranging in age from 35 to 59 years with an average of 46 years having an average duration of symptoms of 4 years duration. Three patients were found by esophagoscopy to have small hiatus hernias of the sliding type. Treatment was with bland diets, antacids and Monodral alone or Monodral with Mebaral. This brought good symptomatic relief to 4 patients, fair relief to 2 patients and poor relief in one patient. Treatment was extended for three months or more depending upon the severity and the response. Two patients had a dryness of the mouth about the third and fourth week and one patient had slight blurring of vision. With temporary reduction of dosage in these cases, tolerance developed and all were able to take the regular 5 mg. of Monodral q.i.d. for the duration of treatment.

Duodenitis

Of the seven patients diagnosed with duodenitis there were 5 males and 2 females with an average age of 45 years and an average duration of symptoms of 5 years. The clinical history and physical findings of epigastric tenderness usually to the right of the midline suggested peptic ulcer. One patient had had a cholecystectomy and three patients appendectomies, all without relief of symptoms. X-ray examination of the upper gastrointestinal tract showed thickened duodenum without evidence of ulceration and palpation gave tenderness and irritability in the area. The colon is negative or may be in various degrees of spasm. Endoscopic examinations are usually negative except for some pylorospasm.

Treatment is the same as for ulcers, namely, Monodral and/or Monodral with Mebaral, a.c. and h.s. which, if continued for several months gives good results. Immediate results are for the most part slower than with ulcers, but the roentgen re-examination months later while usually showing considerable improvement, especially with regard to spasm, irritability and tenderness, may still show some thickening and deformity. One 52-year old female who experienced a dry mouth and blurring of vision discontinued the medication. Otherwise the other patients experienced no difficulty with their medication.

Hypertrophic Gastritis

As with duodenitis, hypertrophic gastritis constitutes an enigma to the clinician, not only from the standpoint of diagnosis but also from the standpoint of treatment. There were eight patients diagnosed by the usual clinical, roentgen and laboratory examinations and after confirmation by gastroscopy treatment was started. Symptoms are variable consisting of epigastric distress, burning

gas, etc., usually simulating ulcers but without the usual periodicity of ulcers. There is much variation in the time of pain in relation to meals without the usual relief from food. There were 6 males and 2 females ranging in age from 38 to 59 years with an average of 46 years and an average duration of symptoms of more than 4 years. There was some dryness of the mouth in three patients but only in one was it sufficiently annoying so as to restrict the medication tc one-half the dose for a few weeks. There were excellent symptomatic responses in 4 patients after 12 to 16 weeks, a fair response in 2 patients, and a poor response in 2 patients. Repeat x-rays of 4 patients showed an excellent response in three. The one fair response showed some improvement with lessened spasm. In one with an excellent response and regastroscoped there was still some evidence of hypertrophic gastritis although it was felt that there was at least 50 per cent improvement. It is felt that the milk-free diet and Monodral were equally responsible for this improvement.

It is a truism that by no means do all patients with gastrointestinal complaints have gastrointestinal disease. Many patients with neuropsychiatric disorders, endocrine disorders, and renal or cardiovascular disease may have as their presenting complaints, symptoms suggestive of gastrointestinal disturbances. The first consideration that the clinician has in dealing with complaints referable to the digestive tract is to try and determine if it is a primary gastrointestinal disease or secondary to some other disease. If after careful examination, spastic disorder is found affecting the digestive tract, the diagnostic problem is still somewhat complicated, inasmuch as this region is particularly sensitive to the emotions through its connection with the central nervous system. Successful management of spastic conditions affecting the antrum, the pylorus and the colon requires careful evaluation of etiological factors. Functional complaints in emotionally unstable individuals usually shows some motor disturbances in the gastrointestinal tract. As adjunctive therapy, spasmolytic drugs have wide application in the relief of this type of visceral spasm. Inasmuch as one therapeutic agent often has the power to potentiate the action of another, and particularly in conditions as described, I have found the combination of Monodral with Mebaral to be a most worthwhile agent in the lessening of the nervous tension as well as the spasm.

Neuromuscular Imbalance

Benign functional disturbances are not incommon and postulate some neuropsychiatric condition which affects various segments of the gastrointestinal tract. Sixty such patients were studied; 15 with roentgenologic evidence of antral and pyloric spasm without other evidence of organic disease in the chest and abdomen; 12 with roentgenologic findings of biliary dyskinesia or poor gallbladder function, and 33 with spastic conditions in the lower intestinal tract. These were treated with Monodral or Monodral with Mebaral as the chief therapeutic agent.

Spastic disorders affecting the antral region and pylorus require careful consideration. Often they have some symptoms suggesting peptic ulceration, and all indications of hyperacidity. Of 15 patients so affected, 10 were males and 5 were females with the youngest 26 and the oldest 59 years leaving an average age of 41 years. After careful clinical investigation and roentgen examination, gastroscopy is indicated in most all such cases in order to determine if organic disease is present. While the symptom-complex is often suspicious of ulcer, chronic cholecystitis is also frequently suspected, yet in none of this series of cases treated with Monodral over the past 30 months have any individuals demonstrated evidence clinically or morphologically that reversed the diagnosis on which their treatment was based. By no available diagnostic methods could ulceration, pancreatitis, or organic disease of the biliary system be demonstrated.

The diet was restricted only in as far as eliminating the type of foods that were inclined to produce gas and distress for that individual including in general all fried, highly seasoned foods and coffee. Antacids were given only in those who evidenced hyperacidity or who were more comfortable from such in the early part of treatment. Monodral with Mebaral was preferred for most of these cases, particularly those who manifested nervous instability. In a few who were particularly sensitive to any type of sedative, dizzy or drowsy, and which could be a definite hazard at work or driving, Monodral in 5 mg. doses was given a.c. and Monodral with Mebaral at bed time. Duration of treatment in one case was that patient who was kept 90 per cent free of the epigastric pain and distress until adjusted. Within one month of the time, he changed his working conditions, was completely relieved of his distress and he was able to get along on an occasional dose.

Eight patients received excellent therapeutic results, four fairly good (they were quite happy and satisfied) and in three the results were poor or unsatisfactory. The best results were obtained in those patients who could take the Monodral with Mebaral over sufficiently long periods of time and make during this time the necessary psychological adjustments. Side-effects were noted by five patients with dry mouth and occasional blurred vision, and in four this was no great handicap as tolerance to the drug gradually reduced the unpleasantness after three or four weeks. In one, the side-effects to Monodral were quite pronounced producing dry mouth, blurring of vision and some bladder atony. The drug was reduced 50 per cent with practically complete disappearance of side-effects, but even after eight weeks, increase to full dose produced some of the side-effects. This patient was handicapped by inability to tolerate full therapeutic doses, not only of Monodral but of several other anticholinergics tried. He was one of three whose therapeutic results was poor.

Twelve patients had attacks simulating cholecystitis displaying functional disturbances described in the roentgen reports as biliary dyskinesia. Some had

in addition, a spastic colon. In this group were nine males and three females. In none could organic disease of the digestive tract account for the symptoms suggestive of hyperacidity, pain, bloating, gas, etc. Food idiosyncrasies undoubtedly accounted for some, while in others a neuromuscular imbalance appeared to be the all important factor. The treatment was in most respects similar to that of patients with spastic colon.

In the other group of neuromuscular imbalance 33 patients whose chief complaints and clinical findings were referable to functional disturbances of the colon were treated with Monodral and/or Monodral with Mebaral. All had irritable spastic colons. Many had some food idiosyncrasy, some had migraine or migraine equivalents, and others had poor gallbladder function. In some of the female patients the colonic disturbance started or became aggravated with the menopause. Many displayed psychoneurotic manifestations. In all patients, in addition to the usual clinical examination and tests, x-rays of the digestive tract with particular reference to the colon, a stool analysis and proctosigmoidoscopic examination was given. The final pretreatment diagnosis was a functional colonic disturbance, and while some seven patients had roentgen evidence of diverticula of the colon and sigmoid, there was nothing evident from previous history, x-ray or other tests and examinations to indicate that the diverticula had been or were inflamed. In practically all there was some evidence of underlying psychoneurosis, and it was felt that the colonic disturbance was the chief somatic expression of a disturbed psyche. Of the 33 patients, 23 were females and 10 were males. The oldest was 62 years and the youngest was 19 years. The average age for the group was 43 years. Because of the relatively high incidence of psychoneurosis in the group, Monodral with Mebaral was the preparation of choice. As was my experience with the other neuromuscular imbalances, it was an excellent antispasmodic and it was used for relief of pain and nervous tension, particularly in the last two doses.

As a rule the Monodral preparation, either plain 5 mg. or in combination is given q.i.d. a.c. and h.s. The duration of treatment varied from three weeks to as long as four months.

Nine patients experienced varying degrees of side reactions during the treatment, usually in the second and third weeks. In five a slight dryness of the mouth was felt until tolerance developed and dosage did not have to be curtailed. In two there was definite dryness of the mouth and some blurring of vision, but this receded when the dose was cut and it was then graduated upward. In two the reaction felt in the mouth and eyes was the same as in the other two, but in addition one became quite constipated, and the other experienced difficulty in voiding. These symptoms largely disappeared after approximately 50 per cent reduction in dosage, but returned to about 50 per cent of original severity when a full therapeutic dosage was resumed. Twenty-two patients who experienced good or excellent results during and for a six month follow-up never were completely relieved, having to take Monodral or some sedatives

and antispasmodics most of the time. Four patients either experienced no appreciable relief or not more than 25 per cent relief during treatment period or in later follow-up.

Summary

Monodral bromide is an effective and well tolerated anticholinergic agent which has been found to be a very useful adjunct in the treatment of approximately 100 patients with benign ulcerations and neuromuscular imbalances of the upper digestive tract over a period of 30 months. It produces marked inhibition of gastric secretion with a resultant reduction of gastric acidity, and it causes a powerful reduction of hypermotility and spasm of the stomach and small intestine. These combined actions reduce pain and promote healing.

In addition to its healing effect on benign ulcers (both duodenal and gastric) Monodral is useful in the treatment of peptic esophagitis, hypertrophic gastritis and duodenitis.

Monodral alone or Monodral with Mebaral (a reliable sedative and antispasmodic) is an excellent therapeutic agent in the neuromuscular imbalances that are found clinically in gastric antral and pylorospasm, biliary dyskinesia and in spastic or irritable colon.

Pretreatment diagnostic criteria and confirmations, methods of treatment and results of therapy with a follow-up of up to 30 months are presented.

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THE MANAGEMENT OF THE PATIENT WITH AN ABDOMINAL ANUS*

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As the result of advances in colon surgery[1-6] more patients are destined to live with an ileostomy or colostomy. The responsibility for rehabilitation must be undertaken by the physician who recommends colectomy. Those who manage limb amputees carefully plan the reconstructive surgery and give detailed

TABLE I

TYPES OF OCCUPATION

Housewife	14
Stenographer	8
Plumber	2
Electrician	2
Painter	1
Carpenter	2
Automobile Mechanic	1
Teacher	2
Soda Clerk	1
Manufacturer	4
Lawyer	1
Tailor	2
Engineer	1
Salesman	5
Printer	1
Retail Shop	3
Student	4
Pharmacist	1
Unemployed	5

instructions in the use of prosthetic devices in order to obtain maximum benefit. Similarly painstaking construction of an efficient intestinal stoma, careful fitting of the bag and instruction in its proper use are basic in the eventual successful management of colon amputees.

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The initial reaction to the suggestion of a permanent abdominal anus is often revulsion. The social stigma attached to fecal incontinence frightens the patient. An important preliminary to surgery, therefore, must be the psychologic preparation. The truth need not be distorted or glossed over. All questions should be answered tactfully and honestly. The development of the relationship between the doctor and patient, leading to mutual confidence and understanding, is necessary. The handicaps of invalidism and decreased life expectancy without surgery are balanced against the relatively unfettered existence of the patient with ileostomy or colostomy. The care of the prosthesis can be compared to the cleaning of the anus after defecation. Failure in adaptation to the abdominal anus can be anticipated if the patient is not prepared before surgery to psychologically accept it.

Ileostomy

The placing of the ileostomy stoma is planned in advance. Depressed scars or bony prominences are avoided so that coaptation of the prosthesis and skin will be snug. The site must not be too low, or flexion of the thighs in sitting will displace the bag. If the stoma is too high, revealing bulges may embarrass the patient. This is particularly true in women in whom the site should be 3 or 4 inches below the waist so that the clothes hang freely. In order to avoid stenosis a button of skin and anterior rectus sheath or external oblique aponeurosis is excised corresponding approximately to the width of the ileum. Six to twelve fine silk sutures are placed to join the posterior rectus sheath and peritoneum encircling the opening. At least 3 cm. of ileum is pulled through the opening and the sutures are taken into the mesoileum. To prevent prolapse the mesentery of the ileum is fixed to the parietal peritoneum. Suture of the mesentery to the anterior lateral and posterior wall to build a complete lateral diaphragm is advised[7]. A cuff is then fashioned by everting the ileum 1½ cm. and fixing it to the surrounding subcuticular fascia and skin. This maneuver prevents retraction and seems to minimize the serositis which can lead to stenosis[8].

Immediately after surgery a standard 16F or 18F catheter is inserted into the stoma and decompression is instituted. Karaya powder or aluminum paste is spread on the skin around the ileum. On the 3rd or 4th postoperative day a bag is fitted over the ileostomy. The Fazio[a] or Pierce[b] bags lend themselves well for this purpose, since they have soft facings and can be cut to fit, without impinging on the bowel.

About 4 weeks after operation the stoma assumes its final size. A rigid faced bag—i.e. Rutzen[c], Torbot[d], or Permatype[e] may now be fitted. Most patients

a. Thomas Fazio Laboratories, Auburndale, Mass.
b. United Surgical Supplies, New York, N. Y.
c. H. W. Rutzen and Sons, Chicago, Ill.
d. Torbot Co., Providence, R. I.
e. Eastern Sales Co., W. Hartford, Conn.

prefer the rigid faced bags. Some, however, prefer the disposable features of the Fazio bag. In fitting the rigid faced bag, an allowance of ¼ inch around the stoma is planned in order to allow for the swelling and edema of the ileum which occurs as the result of various dietary and emotional stimuli. The forcing of a swollen stoma into too narrow an opening injures the bowel and may result in formation of a fistula or amputation of the exteriorized segment.

The tremendous loss in sodium, potassium and chloride immediately after surgery is replaced. Salt is given liberally, otherwise weakness and abdominal cramps may be very distressing. The diet should be high in protein and low in fat. Because of its choleretic action fat seems to cause hypermotility and diarrhea. Hard sugar candies are well tolerated, but chocolate may cause dysfunction. Leafy vegetables high in cellulose, form bezoars and, like leaves in a drain, clog the stoma. Nuts, raw fruits, raisins, apricots and berries are also poorly tolerated. Smoking and cocktails are allowed.

TABLE II

ECONOMIC ADJUSTMENT

Less than 1 week lost in 1 year	35
Less than 3 weeks lost in 1 year	18
Less than 5 weeks lost in 1 year	3
Unemployed	4

The patients learn to care for the skin and stoma, and to use the prosthesis properly before leaving the hospital. The stoma is dilated to the proximal digital articulation of the 5th finger each time the bag is changed. This maneuver should be discouraged, however, if it proves to be traumatic. The bag may be worn for 2 or 3 days, or until the margins begin to separate from the skin. Snug adherence of the bag to the skin is important. Leakage results in skin excoriation. If this occurs, karaya gel or Desitin powder may be placed over the abraded skin and the device can then be cemented to the area. The best time to change the bag is before breakfast, when intestinal motility is minimal. Bathing can be accomplished at this time with the least danger of involuntary discharge from the ileum.

A full life can be lived with an ileostomy. The patients with ileostomy have many vocations (Table I) and work regularly. Of 60 patients followed 1 to 8 years after colectomy, 53 had lost less than 3 weeks work time in a year. Only 4 were unable to work because of poor adaptation to the ileostomy (Table II). These 4 patients had to seriously restrict their diet but 38 patients ate self-selected full diets (Table III). Unrestricted social life was possible in 40 patients, with 10 actively courting. Only 4 were severely restricted. Swimming,

tennis, golf, bowling, dancing and even football are some of the physical endeavors undertaken by these patients.

Colectomy for ulcerative colitis does not lead to impotence or frigidity, as it frequently does following rectal resection for carcinoma. Sexual function is good in 27 patients. 5 patients have conceived and delivered since ileostomy and 3 wives of husbands who have colectomies have been delivered of normal babies. Frigidity occurred in 6 and impotence in only 2 patients. Frigidity or impotence of the partner occurred in 4 instances (Table IV).

The patients' reaction to ileostomy is shown in Table V. Thirty-six of 60 patients were highly satisfied with the results and enjoyed full economic and

TABLE III

SOCIAL ADJUSTMENT

A. Eating Habits	
Full diet	38
Restrict vegetables	12
Restrict milk	3
Restrict fat	3
Restrict diet to pureed food	4
B. Social Relations	
Unrestricted	40
(10 actively courting)	
Worried about odor	10
(2 actively courting)	
Tendency to limit activity	6
Marked restriction of activity	4
C. Athletics	
Swimming	25
Tennis	10
Dancing	35
Golf	6
Bowling	4
Football	1

social rehabilitation. Seventeen were satisfied and rehabilitated economically, but were sensitive to the odor. Only 3 regretted the ileostomy. These patients had recurrent complications and were invalids.

COLOSTOMY

Generally, permanent colostomy is performed for carcinoma. Since these patients are older there is less resistance to the abdominal anus. Psychologic preparation is not essential.

A low residue diet is prescribed for 5 days before surgery. The colon is cleansed by catharsis and daily saline irrigations for 3 days before operation.

A combination of 2 gm. of Neomycin and 1 gm. of oxtetracycline in 24 hours has been found to be most effective in diminishing the colonic bacteria[8]. Intestinal sterilization is begun 2 days prior to operation.

By adherence to surgical principles complications of colostomy are minimized[9]. The bowel is brought out about 2.5 cm. above the surface of the skin to prevent retraction. Too long a loop is undesirable. In order to avoid slack within the peritoneal cavity the bowel is pulled out as far as the mesenteric attachments permit. The blood supply to the colostomy must be carefully preserved. Rough handling may injure the bowel wall or produce ischemia. The colostomy should fit snugly, but not tightly through the incision, allowing about one finger clearance.

The preferred site for the permanent abdominal anus is the sigmoid colon, because the fecal material discharged is less irritating to the skin, more solid

TABLE IV

SEXUAL ADJUSTMENT

Good		27
Conceived and delivered		5
Wives of patients delivered		3
Impotence		2
Frigidity		2
Avoided coitus		9
	Self-conscious Weakness	
Refused to answer		14
	Unmarried Self-conscious	

in consistency and easily controlled. Some prefer to bring the colostomy to the outside through the upper end of the exploratory incision, usually a left paramedial one, by placing the bowel just below the umbilicus. Our results have been excellent wtih a low left rectus colostomy, through a counter incision. This has the advantage of not infecting the operative wound, thereby minimizing the incidence of stricture in the colostomy opening and reducing the danger of pericolostomy hernia. No sutures are placed in the wall of the gut. as a safeguard against pericolostomy abscess. The occluding clamp, and gauze, lightly packed about the wound, is sufficient to prevent retraction of the bowel. If further fixation is desired the *appendices epiploicae* may be secured to the skin. The mesentery is sutured to the lateral abdominal wall to prevent herniation of the small intestines. The colostomy is carefully examined for viability before the dressing is applied and again a few hours after surgery. If at operation an unusual degree of distention is noted, a Daniel's clamp is applied and a catheter inserted in the opening.

The occluding clamp is usually removed and the bowel opened in 36-72 hours. The patient is assured that the colostomy will shrink and he may be shown how it will look in the future by a former patient. As soon as possible after the first bowel movement, which usually occurs on about the fifth day, the patient is familiarized with the technic of irrigating the colostomy. The irrigation is first administered by the doctor or trained nurse. We had used the Patten Colostomy Irrigator[f] for several years with excellent results. It requires a minimum of assembling, performs its function well in a minimum of time, is easily cleaned and quite safe to use. The tip, shield and trough is made of plastic and requires cleansing with only hot water and soap. The bowel cannot be penetrated by the introducer, as has happened with catheter tips. The backflow and leakage is prevented by the shield which fits tightly about the colostomy opening. The enema bag is held about 18 inches above the stoma or attached

TABLE V

ADJUSTMENT TO ILEOSTOMY

Patients' Reaction:	
Highly Satisfied	36
Full economic and social rehabilitation.	
Satisfied	17
Full economic, poor social adjustment. Sensitive about odor.	
Dissatisfied	4
Odor, fistula, and complications. Impotence.	
Regret ileostomy	3
Skin excoriation, cramping, fistulae. Ascending ileitis. Unable to adjust.	

to a fixed place on the wall. With the patient sitting on a stool in front of the watercloset, about a quart of warm water is introduced into the colon, after the tubing has been cleared of air. The water is forced through the bowel in a steady even flow. The complete washing out of the bowel contents usually takes from 20-30 minutes. If the patient is especially constipated, the water is fed into the colon in stages to prevent cramping. The shield is held tightly against the stoma and retained in this position for 2 or 3 minutes before release. The contents empty into the bowl through the plastic trough, which is maintained securely against the body by an adjustable strap. The irrigation is performed daily in order to inspire confidence in the new excretory modality. It is performed at the same time each day, at the convenience of the patient. In a short time, the patient realizes that this practice is nothing more than a simple enema and that cleanliness and regularity can easily be maintained. Many other good

f. Patten Irrigator Co., Wilton, Conn.

irrigating apparatuses are available, but in our experience this method appears to be the simplest and safest.

With adequate training, a colostomy bag is unnecessary as a routine prosthesis. A disposable shield[g,h] may be used, however, in cases of diarrhea, or for security, while working at certain occupations requiring bending, stretching or pulling. These devices may also be used while travelling or when routine bowel care is not possible.

The diet of the patient with colostomy need not be restricted. The patient's individual bowel habit determines the amount of laxative fruits he may eat. If loose stools occur, rice and low residue foods form the main dietary segment.

The process of rehabilitation continues after discharge. The demonstration of technics must be individualized. Expert supervision, patient counselling and thorough indoctrination are essential to the success of the rehabilitation program. The cooperation of former patients, to transmit their experiences to new patients, is used to make adjustment easier. An intestinal rehabilitation clinic is a great help in managing patients with ileostomy. By observing the patients, physicians have learned a great deal about management of the abdominal anus. No longer should one look upon colostomy or ileostomy as a gross disability. With proper training it is much less disabling than a limb amputation.

Summary

1. The management of the abdominal anus depends on good psychological orientation.

2. The procedure and location of the stoma should be planned before surgery to minimize prosthetic difficulties.

3. A proper prosthesis and education in its use are essential before the patient is discharged.

4. Sympathetic counselling, demonstrations by previous patients and proper supervision make rehabilitation more complete.

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Discussion

Dr. Theodore S. Heineken (Bloomfield, N. J.):—I should like to ask Dr. Fierst whether he has had any success with skin-grafting of the ileostomy stump.

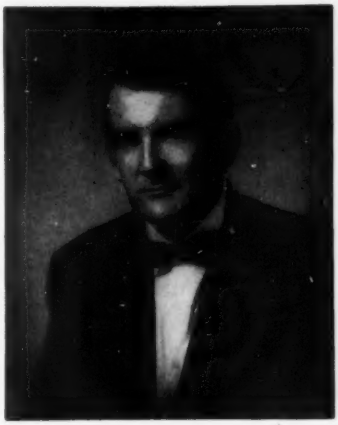
Dr. Fierst:—In regard to skin-grafting of the stump, we feel it is unnecessary. I think that a good normal mucosa, when exposed to the ileal contents, is much more resistant to the action of ileal digestion than is the skin. I think the less manipulation to which the stump is subjected, the less chance one has of developing cicatrization and stenosis.

I believe that the patient on whom skin-grafting procedures were done on the ileostomy did not do as well as those with the procedure as outlined in the paper.

In Memoriam

We record with profound sorrow the passing of Dr. Elihu Katz of New York, N. Y., Life Fellow and esteemed Treasurer of the American College of Gastroenterology and Dr. F. H. Bowman of Bronxville, N. Y., Associate Fellow of the American College of Gastroenterology. We extend our deepest sympathies to the bereaved families.

Tributes to the late Dr. Katz will be published in an early issue of The American Journal of Gastroenterology.



President's Message

The progress of the American College of Gastroenterology is a measure of our service to the profession. Our organization has received criticism from many quarters and this to me is encouraging. It means that the American College of Gastroenterology is becoming an increasing force in medical circles. Any institution that merits continual approbation is usualy decadent rather than progressive.

It is my opinion that our organization should expand more into the field of gastroscopy and should encourage the formation of gastroscopic services in clinics and hospitals in all of the larger communities. The pharynx and esophagus have for a long time been considered border states and interest has been shared between gastroscopists and otorhinolaryngologists. As a result of this medical conflict, relatively few advances have been made in the fields of physiology and surgery of the pharynx and upper esophagus. As many of us feel these are properly the realm of gastroenterology, we should encourage our members to expand their interests in this direction.

In the southern states there is an urgent need for postgraduate instructions at the colored hospitals. Dr. Irving A. Levin in New Orleans has developed a program of weekly scientific meetings with the staff of Flint-Goodridge Hospital, sponsored by the Louisiana members of the American College of Gastroenterology. The degree of service we render our medical confrères will act as indicator of our future success.

I. J. Nix

ABSTRACTS FOR GASTROENTEROLOGISTS

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GASTROINTESTINAL TRACT

PHEOCHROMOCYTOMA AS A MASSIVE ABDOMINAL TUMOR: Bentley P. Colcock and James E. Hull. Indiana State M. A. 48:955 (Sept.), 1955.

The authors present a case report of a very large pheochromocytoma which weighed 360 grams after the removal of 4,000 to 5,000 c.c. of thick, viscid fluid.

The patient had presented himself with no other symptoms or findings other than a gradual abdominal enlargement. However, during operative manipulation of the tumor the hypertensive episode resulted. The authors feel that pheochromocytoma should be suspected if a mass of unknown etiology appears to arise from the region of the left renal pedicle and particularly if manipulation produces a hypertensive crisis.

JOSEPH E. WALTHER

VISCERAL INJURY RESULTING FROM NONPENETRATING ABDOMINAL TRAUMA: Grover C. Penberthy and Charles R. Reiners. J. Michigan M. Soc. 54:1057 (Sept.), 1955.

Abdominal injury due to blunt trauma in auto accidents are often overlooked in the initial examination. Serious intraabdominal injury may be sustained from a relatively minor blow.

In cases where the diagnosis of intraabdominal injury is in doubt, the patient should be examined frequently. If after the six hours there is persistent abdominal pain, spasm and tenderness, a laparotomy should be performed. Treatment for shock if present is of course of first consideration.

Fractured ribs in the lower chest raise the possibility of ruptured spleen or liver. Free air in the abdominal cavity is conclusive evidence of a perforated bowel. Air in the retroperitoneal tissues as seen by x-ray may indicate rupture of the second or third part of the duodenum. Obliteration of normal psoas or renal shadow by a diffuse haze indicates fluid which in traumatic cases is probably blood.

The authors make a plea for early intervention before irreversible complications appear with unheralded speed.

A. J. BRENNER

THE MANAGEMENT OF INCARCERATED HERNIAE IN INFANTS AND CHILDREN: George H. Nip. Hawaii M. J. 15:30 (Sept.-Oct.), 1955.

The author cites from a series of 129 inguinal herniorraphies on the surgical service of Kings County Hospital, Brooklyn performed on 106 children. There were 95 males and 11 females, 52 occurred on the right and 28 on the left, 48 were bilateral, all were indirect, 26 being scrotal. Associated congenital anomalies were common, 36 per cent having either hydrocele, undescended testicles, congenital heart defects, cleft palates, spinal meningoceles, club-foot and umbilical herniae. Incarcerations—18 per cent, mostly in the first six months. There were no strangulations in this series. Successful reduction was accomplished in 78 per cent, and an interval of 2-5 days allowed before herniorraphy was performed. A second group of 22 per cent having incarceration with suspected strangulation was subjected to immediate operation and these had a morbid postoperative course with a longer hospitalization due to wound and respiratory complications, ileus and distention.

LOUIS K. MORGANSTEIN

ESOPHAGUS

MISLEADING X-RAY ASPECTS OF MEGAESOPHAGUS: Maurice Bariety, Charles Coury, Jean Acar and Miss Rampon. La Semaine des Hopitaux 31:2023-2033 (10 June), 1955.

The authors give a full description of the different radiological features of megaesophagus. This condition may appear, according to cases, as an abnormal shadow, a localized area of translucency, or both combined with fluid level.

The opaque type of picture is that of a dark vertical stripe, with bilateral or right-side only widening of the mediastinal shadow. This abnormal density is located on a posterior plane, while the trachea is displaced forward. The shadow is more often homogeneous than mottled, the later case being connected with the permanence of particles of food in the enlarged lumen. There may be a moderate stricture of the shadow above the hilar level, giving an hour-glass picture. This type of esophageal shadow has two main features: it extends from the upper chest-opening down to the diaphragm and its lateral margin, either straight or bulging, is sharply defined. Lobulated, localized or round-shaped tumor-like shadows are fairly infrequent.

The rarefaction type of picture is very infrequent. Its location is always paramediastinal and suprahilar. It may lead to confusion with lung cavities, cysts or abcess, with hernia or emphysema of the mediastinum.

The fluid-level type combines both previously described pictures: a permanent or variable horizontal line of level is a very valuable x-ray symptom of megaesophagus.

The different types are liable to changes from day to day, according to the state of repletion or emptiness of the enlarged esophageal lumen.

MANAGEMENT OF CORROSIVE BURNS OF THE ESOPHAGUS: John Borrie. Australian & New Zealand J. Surg. 25:62-69 (Aug.), 1955.

The authors divide esophageal burns into three distinct phases: 1. the acute phase of two weeks' duration with superficial necrosis. 2. the intermediate phase following a slough from stage one in which there remains red granulations covering a tubular ulcer. 3. the final phase in which there is replacement of fibrous tissue. The management of the acute and intermediate phases concerns neutralization of the chemical agent, relief of symptoms, maintenance of nutrition, counteraction of the infection and the prevention of stricture formation. The most important thing is to maintain an esophageal lumen. When a stricture occurs the aims of treatment are: to dilate the stricture and if that fails to restore esophageal continuity by surgical means.

BERNARD J. FICARRA

STOMACH

CARCINOMA OF THE STOMACH—SEVEN-YEAR REVIEW: John F. Sanabria. Bol. Asoc. med. Puerto Rico 47:279 (July), 1955.

Sanabria reports on 77 cases of carcinoma of the stomach, 76 of whom were operated on during a period of seven years. Fifty-four and five tenths per cent of the lesions were located in the antrum (area from the angulus to the pylorus), 10.4 per cent at the pylorus, 2.6 per cent on the greater curvature, 9 per cent in the body, and 13 per cent in the fundus of the stomach. Of the total lesions involving the antrum and pylorus (65 per cent or 49 lesions) 20 of these showed obstruction clinically and/or radiologically. Men predominated in the ratio of two to one; the preponderance of age was in the 7th decade, but 5 patients were between 21 and 30 years of age. Gastric analysis with histamine stimulation was performed in 33 patients, in 15 of whom achlorhydria was present. Epigastric distress and pain were the leading symptoms. being present in 63.5 per cent of patients. Dysphagia was present in 9 per cent (note 13 per cent of involvement of the fundus); hematemesis in 5 per cent; nausea and vomiting in 4 per cent. Seventy-six patients were operated on; in 9 nothing was done (exploratory); in 18 a purely palliative procedure was carried out; in 49 a resection. In 25 of the 76 cases, lymphatic glands were involved in metastasis. Of the 49 resected cases, total gastrectomy was done in 13. Attention necessarily centers on these 49 cases, as these had a definitive operation with hope of "cure"—however the follow-up in these cases was in many instances too short or too few in number to allow of conclusions. Nine patients were operated on five or more years ago, of whom 4 lived more than five years. Percentagewise, 12 per cent were explored only; 23.7 per cent were treated by a palliative operation; and 64 per cent by a definitive operation.

SAMUEL L. IMMERMAN

REVIEW OF FIFTEEN YEARS' EXPERIENCE WITH GASTRECTOMY IN A COMMUNITY HOSPITAL: II CANCER: Paul R. Hinchey. New England J. Med. 253:226 (11 Aug.), 1955.

A small series of 46 gastrectomies for cancer of the stomach is reported from a community hospital. Operative mortality for the past 15 years was 31 per cent and has been steadily reduced to 8 per cent in the last 4 years. Five-year cure rate is only 4 per cent. Since no other form of treatment except surgery is of any value in this condition, the authors implore the modern surgeon to be equipped to handle such procedures as total gastrectomy, thoracoabdominal gastrectomy and compound gastrectomy (resection of stomach and adjacent organs involved).

Gastric carcinoma tends to metastasize early and widely by direct extension, by lymphatic and blood vessel invasion and by gravity seeding of the peritoneum. In order to increase the number of resectable cases the author suggests the following: 1. Precursors of gastric carcinoma must be observed more closely and operated on more often. 2. All gastric polyps should be operated on immediately on discovery (35 per cent of gastric polyps have proved to be malignant). 3. Routine gastric extraction for acidity and cytologic study (incidents of cancer in patients with pernicious anemia is 10 per cent). 4. Gastroscopy should be done more often. 5. Immediate surgery for most gastric ulcers. 6. Occasional exploratory laparotomies should be performed in patients with anacidity and mucosal irregularity in whom a final diagnosis cannot be made by x-ray.

A. J. BRENNER

INTESTINES

CLINICAL AND MICROBIOLOGIC ASPECTS OF SALMONELLOSIS: George M. Eisenberg, Anthony J. Palazzolo and Harrison F. Flippin. New England J. Med. 253:90 (21 July), 1955.

The author presents a series of 95 cases of proved Salmonellosis encountered in the Philadelphia General Hospital from 1947-1950. The series comprised 55 adults and

40 children ranging in age from 9 days to 7 years. Negroes comprised 77.5 per cent.

Most common symptoms were fever, and diarrhea. Roseola and splenomegaly was infrequent. Anorexia and weight loss was more common in children than adults. Associated disease was varied and often the actual cause of hospitalization. Mortality was 11.6 per cent with the causes being detailed by the author. In this series 5 patients were carriers and one asymptomatic.

Recovery was in 16 patients with only supportive treatment and no antibiotics. Fifty-one patients received more than one antibiotic including sulfas, penicillin, streptomycin, chloramphenicol, chlortetracycline, and oxytetracycline.

In conclusion the author points out that Salmonellosis is of interest to the surgeon too, being misdiagnosed for appendicitis, cholecystitis, salpingitis, etc.

LOUIS K. MORGANSTEIN

EFFECTS OF MILLION VOLT IRRADIATION ON THE GASTROINTESTINAL TRACT: Irving B. Brick. A.M.A. Arch. Int. Med. 96:26 (July), 1955.

The effect of supervoltage irradiation on the normal gastrointestinal tract of 96 young male adults treated for testicular tumors are described. The patients survived five and more years after the x-ray treatment which was delivered to the middle of the abdomen and lower back and involved the gastric antrum, parts of the liver, the small bowel and the transverse colon. The sensitivity of the individual patient varied markedly. Onset of symptomatology was delayed but occurred earliest in those cases in which the stomach was injured. Radiation dyspepsia with objective findings, gastritis and ulcers with or without perforation and narrowing of the antrum occurred. Even in largest dosage irradiation over the antrum had no effect on the acid secretion during the entire period of observation.

Small bowel changes consisted of nonspecific x-ray deviations, such as thickening of the mucosa, segmentation and clumping, however, in some cases obstruction and perforation occurred. There was also mesenteric fibrosis with decreased mobility of the small bowels and adhesions between them. Colon showed partial and incomplete obstruction. Some cases of necrosis as well as fibrosis of the liver were observed, others with fibrotic shrinking of the bile ducts. Safe maximum tolerance dose was 4000 r for the gastric antrum, 4500 r for the bowels and 5000 r for the liver.

H. B. EISENSTADT

LACTOBACILLUS ACIDOPHILUS TABLETS IN THE THERAPY OF VARIOUS INTESTINAL DISORDERS: A PRELIMINARY REPORT: Asher Winkelstein. Am. Pract. & Digest. Treat. 7:1022 (July), 1955.

The author reports preliminary results on the influence of *Lactobacillus Acidophilus* in varied intestinal disorders. The organism is known to be nonpathogenic and can thus be given with impunity for prolonged periods. The method of treatment used by the author consisted of giving three tablets (100 billion organisms) daily for 6 to 8 weeks, then remitting for about two weeks and reinstituting the same dosage for another 4 to 8 weeks. In some cases as many as 9 to 12 tablets were given daily. In the group of 57 patients with intestinal disorders thus treated good clinical results were obtained in chronic constipation, functional diarrheas, mucous colitis, sigmoid diverticulitis and antibiotic colitis. The treatment was of no value in ulcerative colitis.

ABRAHAM J. BRENNER

RECTAL BLEEDING: Harry Goldman and Max D. Goldman. Clin. Med. p. 681 (July), 1955.

The authors stress the importance of rectal bleeding and the necessity of proctosigmoidoscopy and barium enema examinations in addition to a good history and physical examination. All the possible causes of rectal bleeding are enumerated including intussusception in children and hemorrhoids and carcinoma in the adult. He mentions all the infectious conditions and pathological conditions which could possibly give rise to rectal bleeding.

JACOB A. RIESE

LIVER AND BILIARY TRACT

EFFECTS OF DIETARY PROTEIN, LIPOTROPIC FACTORS AND RE-ALIMENTATION ON TOTAL HEPATIC LIPIDS AND THEIR DISTRIBUTION: C. H. Best, W. S. Hartroft, C. C. Lucas and Jessie H. Ridout. Brit. M. J. 4928:1439 (18 June), 1955.

This study was done on rats. For complete protection of the liver cells in the portal region, the amount of necessary protein depends upon its nature: fibrin is much more effective than casein which is better than soya protein. The effect of protein on the hepatic cells around the central veins appears to be attributable to a large extent to its content of choline-methionine. These observations may help to resolve the discrepancy as to the distribution of liver fat and to the lack of response of certain types of dietary fatty livers to the lipotropic agents used clinically. In Kwashiorkor, the stainable fat is found predominantly in the periportal regions.

IRVIN DEUTSCH

MASSIVE HEPATIC NECROSIS: Jack Gardner. Med. Times 83:585 (June), 1955.

Clinically, massive necrosis occurs in two stages: initial and icteric. The initial stage lasts 6 to 14 days during which fever is present in about 15 per cent of the cases. The general symptomatology consists of: general fatigue, anorexia, nausea and vomiting, with abdominal pain. Loss of appetite may be extreme so that even the sight of food is repulsive. About 16¾ per cent develop jaundice in the early stage but more often there is a two-week interval before icterus becomes manifest. When this develops it is intense and deep orange in color and fluctuates in intensity. Pain over the liver and flank is frequent, but anorexia and muscular asthenia are the most outstanding findings, accompanied by mousy breath. If tachycardia, out of proportion to the fever, develops it is an ominous sign.

A universal finding in hepatic necrosis is a tendency to bleed, especially from the gums and under the skin. Any slight trauma is apt to result in inordinate hemorrhage. Fever is also constantly present, ranging between 100° and 103°.

Physical signs are important. A remarkable symptom is progressive decrease of liver size, noted by percussion day by day. A large liver is incompatible with hepatic necrosis. Ascites occurs if death does not intervene in the first few days, preceded by puffiness of the face with dependent edema. The terminal stage is characterized by drowsiness, coma and nervous symptoms. Paralyses and speech difficulties may occur. Sleep becomes more and more profound. with the patient finally becoming relaxed and flaccid as deepening coma heralds death.

REGINALD B. WEILER

PANCREAS

TREATMENT OF PANCREATITIS: Mandred W. Comfort. A.M.A. Arch. Int. Med. 95:735 (May), 1955.

Treatment of acute pancreatitis consists in controlling the pain by drugs relaxing the sphincter of Oddi such as nitroglycerine, grain 1/100 sublingually, or papaverine, grain 2 orally. Unfortunately, morphine and demerol must be added for their strong analgesic effect in spite of their increase of the sphincter spasm. The maintenance of normal fluid and electrolyte balance is adjusted according to clinical and laboratory findings. This may require addition of water, sodium, potassium, calcium, chloride and bicarbonate. Continuous gastric aspiration avoids stimulation of the pancreas by the gastric juice and decreases the ileus. Shock is usually present and must be treated with whole blood, human serum albumin or Dextran while plasma should best be avoided. There might be a place for corticotropin and cortisone. Infection has to be combatted with terramycin or Aureomycin given in oral doses of 500 to 750 mg. every six hours or in intravenous infusions 500 mg. added to 200 c.c. of normal saline every 12 hours. In addition, a daily dose of one million units of penicillin with 1 gm. of di-

hydrostreptomycin should be given. Atropine grain 1/100 with ephedrine grain ¾ subcutaneously every three hours may also be administered for the suppression of pancreatic secretion. Surgical therapy should be restricted to paravertebral sympathetic procaine or alcohol blocks, drainage of abcesses and pseudocysts and care of acute biliary complications. Chronic pancreatitis requires a high caloric bland diet with 120 gm. of protein and 70 gm. of fat and concentrated triple strength pancreatin in doses up to 5 gm. (15 capsules) with each meal; one multiple vitamin capsule should be added. Surgical treatment of chronic pancreatitis consists of cholecystectomy which is performed only in case of definite gallbladder pathology, prolonged drainage of the common duct, choledochoduodenostomy, cholecystenterostomy, transduodenal sphincterotomy and pancreaticolithotomy.

H. B. EISENSTADT

BENIGN DISEASES OF THE PANCREAS: Charles B. Puestow: Mississippi Valley M. J. 77:89 (May), 1955.

The author reviews the differential diagnosis of acute and chronic pancreatitis, pancreatic cysts, and pancreatic lithiasis. There is a discussion of surgical technics which may be of value to the surgeon. The importance of relieving pain in pancreatic disease is emphasized, since these patients may become drug addicts.

ABE ALPER

PSEUDOCYSTS OF THE PANCREAS: J. Wesley Brander and Robert C. Laird. Canad. M.A.J. 72:910 (15 June), 1955.

Five proven cases of pancreatic pseudocyst are treated surgically by marsupialization. Cure occurred in all cases. The etiology suggested is pancreatic necrosis following acute pancreatitis in four cases and postoperative pseudocyst formation due to trauma following cholecystectomy for chronic cholecystitis with stones in one case.

JACOB A. RIESE

STUDIES ON URINARY LIPASE: Martin M. Nothman, Joseph H. Pratt and Allan D. Callow. A.M.A. Arch. Int. Med. 96:277 (Aug.), 1955.

This is a second report on urinary lipase. The first one presented evidence of its pancreatic origin on the basis of investigations in dogs. This second study was conducted with the urines of 100 healthy humans. The enzyme was found to be constantly present in these individuals in values varying from 0.1 to 0.75 units per c.c. of urine. Fasting state and food intake had no significant influence on the concentration or the urinary lipase. Very slight variations were obtained in one individual during the various periods of the same day as well as on several consecutive days. Normal total output in 24 hours ranged from 200 to 800 units. No abnormalities of serum lipase were found during normal pregnancy.

H. B. EISENSTADT

BOOK REVIEWS FOR GASTROENTEROLOGISTS

PREVENTION OF DISEASE IN EVERYDAY PRACTICE: Isadore Givner, B.S., M.D., F.A.C.S., Associate Clinical Professor of Ophthalmology, New York University Postgraduate Medical School, Director of Ophthalmology, New York City Hospital, etc., etc., and Maurice Bruger, M.Sc., M.D., C.M., F.A.C.P., Associate Professor of Medicine New York University Postgraduate Medical School, Attending Physician and Director, Department of Clinical Pathology, University Hospital, Visiting Physician, Bellevue Hospital. 964 pages with 50 illustrations, frontispiece in color. The C. V. Mosby Co., St. Louis, Mo., 1955. Price $20.00.

In addition to the authors, numerous contributors have added valuable material to this well written, well printed and illustrated book. A total of 37 chapters, extensive references and index enhance this ready reference volume.

Givner and Bruger's "Prevention of Disease in Everyday Practice", presents the material relevant to the diagnosis and management of clinical disorders in such a lucid and succint manner, that no physician or surgeon could afford to be without this edition.

1954-1955 YEAR BOOK OF PATHOLOGY AND CLINICAL PATHOLOGY: Edited by William B. Wartman, B.S., M.D., Morrison Professor of Pathology, Northwestern University, etc., Chicago, Ill. 486 pages, illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1955. Price $6.00.

As in previous years, the Year Book of Pathology and Clinical Pathology covers the entire field of medicine including surgery and the specialties. The section on clinical pathology includes hematology, microbiology and clinical chemistry. The section on clinical chemistry discusses the electrolytes, electrophoresis, enzymes and miscellaneous topics, bringing the physician up to date on the newer procedures and findings.

It is highly recommended to all physicians and advanced medical students.

SANDOZ ATLAS OF HEMATOLOGY: 91 pages, illustrated in color. Sandoz, Ltd., Basle, Switzerland, 1952. Price $7.00.

A looseleaf text in three parts, extensive literature, references including tables and record forms.

Authors of text books and other literature describing hematological findings in normal and abnormal states should take notice of this beautifully prepared and executed loose-leaf manual.

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The illustrations as well as the accompanying descriptions are clear and add a great deal to the value of this manual.

The reviewer recommends it highly.

STRATEGIE ET TACTIQUE EN CHIRURGIE ABDOMINALE D'URGENCE (STRATEGY AND TECHNIC IN URGENT SURGERY): Charles Clavel, Assistant Professor, Faculty of Medicine of Lyon, France. 580 pages with 37 illustrations. Masson & Co., Paris, France, 1955. Price 3.200 fr.

In the eight chapters, the author stresses the fact of early diagnosis, intervention, findings, complication and sequelae of the acute abdomen. It is a well written and printed volume with insufficient illustrations. There is a good index and adequate references.

Surgeons who read French will find instructive material and advice in this volume.

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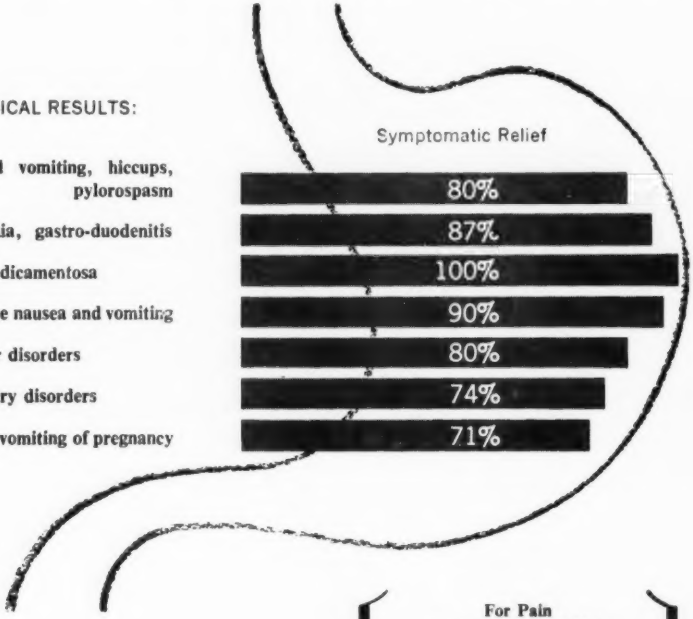

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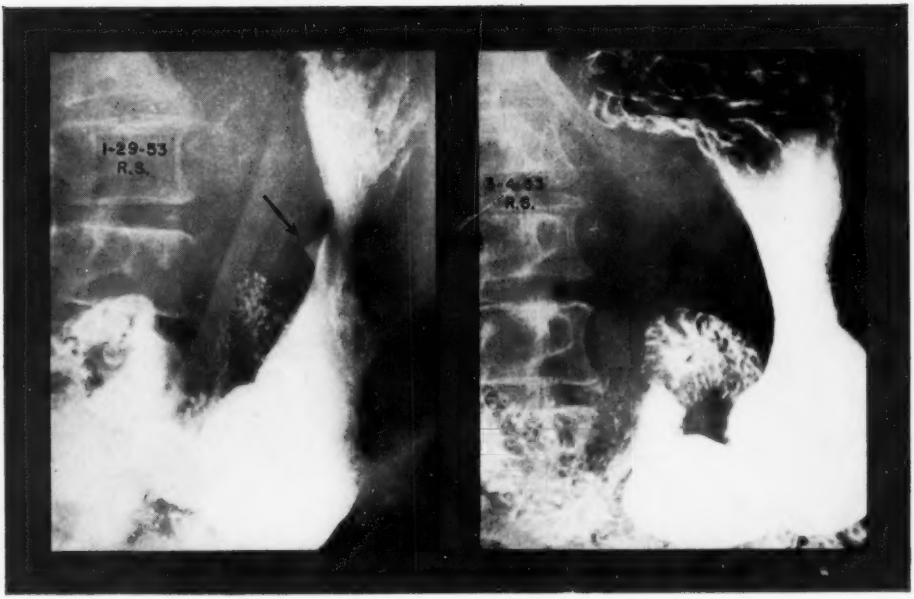

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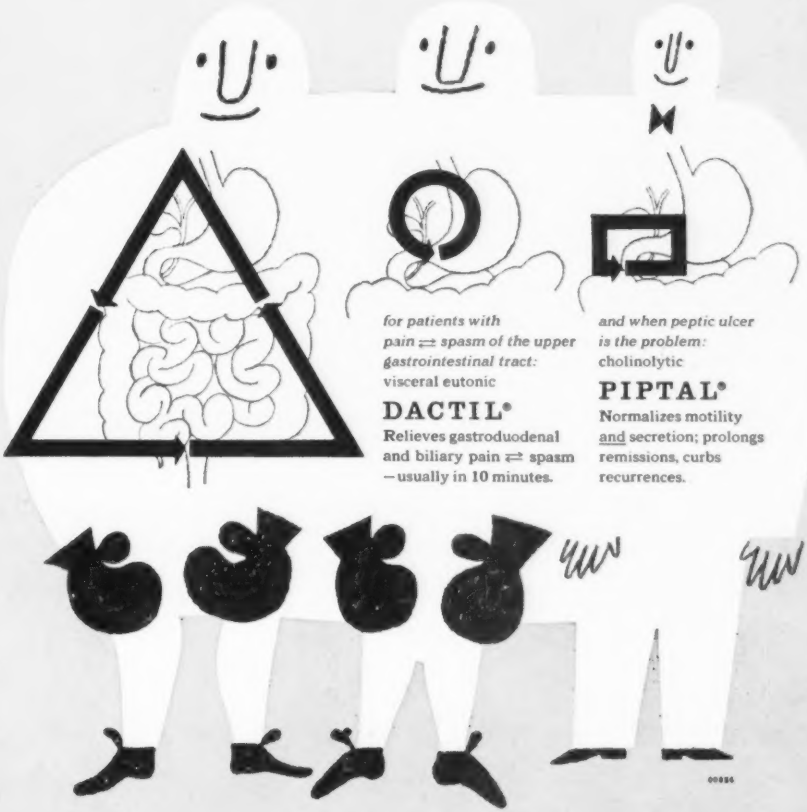
three patients...three piperidols

favorite for generalized G.I. dysfunction

TRIDAL

paired piperidol action

gives rapid, prolonged relief throughout the G.I. tract



for patients with pain ⇄ spasm of the upper gastrointestinal tract:
visceral eutonic

DACTIL®

Relieves gastroduodenal and biliary pain ⇄ spasm—usually in 10 minutes.

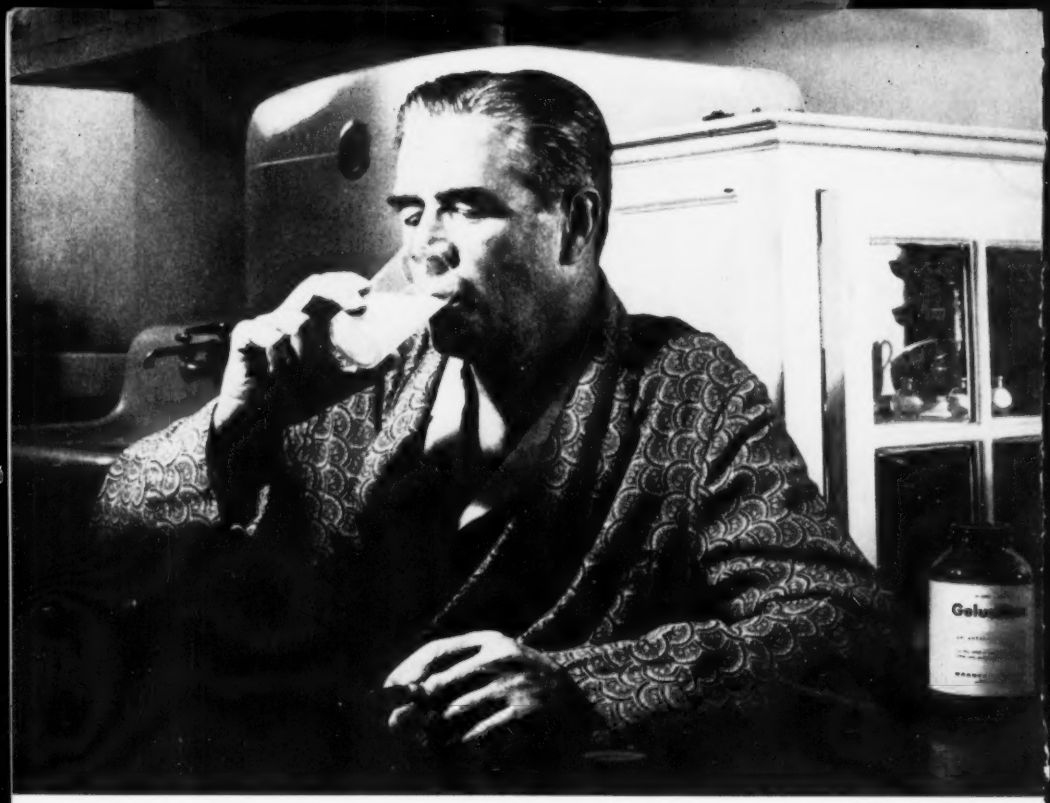
and when peptic ulcer is the problem:
cholinolytic

PIPTAL®

Normalizes motility and secretion; prolongs remissions, curbs recurrences.

Patients on TRIDAL, DACTIL or PIPTAL remain singularly free of anticholinergic-antispasmodic side effects.

LAKESIDE



to pass "the acid test" day and night

Gastric hyperacidity checkmated: Acute or chronic gastric hyperacidity can now be held in check both day and night, with Gelusil and the new formulation, Gelusil-Lac.

Sustained daytime antacid protection: The sustained action of magnesium trisilicate and specially prepared aluminum hydroxide gel restores and maintains the gastric pH within the normal range, without overneutralizing or alkalizing. Gelusil thus avoids the twin dangers of acid rebound and systemic alkalosis.

Extended nighttime protection: Gelusil-Lac combines the proven antacid action of Gelusil plus the sustained buffering effect of specially prepared high protein (low fat) milk solids. The formula is designed to *prevent* the onset of gastric pain at night, especially "middle-of-the-night" attacks.

Nonconstipating: Gelusil's aluminum hydroxide component is of a low order of chemical reactivity, hence the formation of astringent — and constipating — aluminum chloride is minimal.

Dosage: 2 Gelusil tablets or 2 teaspoonfuls of Gelusil liquid two hours after eating or when symptoms are pronounced. Each tablet or teaspoonful provides: 7½ gr. magnesium trisilicate and 4 gr. aluminum hydroxide gel. Gelusil-Lac: at bedtime, one heaping tablespoonful stirred rapidly into one-half glass (4 fl. oz.) of cool water. (Provides equivalent of 4 Gelusil tablets.)

Gelusil®/Gelusil-Lac

WARNER-CHILCOTT